

IN VIVO X-RAY FLUORESCENCE ANALYSIS FOR MEDICAL DIAGNOSIS

**A non-invasive method for quantitative
determination of kidney function after
radiographic examinations with iodinated
contrast media**

Thomas Grönberg



Lund and Malmö

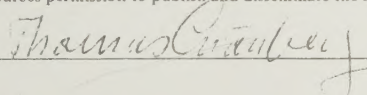
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Title and subtitle IN VIVO X-RAY FLUORESCENCE ANALYSIS FOR MEDICAL DIAGNOSIS. A non-invasive method for quantitative determination of kidney function after radiographic examinations with iodinated contrast media.			
Abstract A Monte Carlo code has been constructed and used to simulate the energy distribution of scattered photons obtained in various <u>in vivo</u> X-ray fluorescence measurements. The structure of this distribution has been investigated and discussed. Studies of the response function of the Ge-detector used have made it possible to convert the calculated scatter spectra to pulse-height distributions. These studies have shown to be valuable tools in designing <u>in vivo</u> X-ray fluorescence measurements. In vivo X-ray fluorescence measurements have been used for quantitative non-invasive measurements of the concentration of iodine-containing contrast media in rabbits without the use of blood or urine sampling. The biological half-life of the contrast medium in the soft tissue part of the nose (measured <u>in vivo</u>) was similar to that in serum (measured <u>in vitro</u>) when determined in the period 2 - 4 hours after injection. This result indicate the possibility of being able to use the method for clinical evaluation of kidney function. The method has been used in patients referred for urography and who had therefore been injected with routine amounts of iodine-containing urographic contrast medium. After urography, the elimination rates of urographic contrast medium from both serum and finger tissue were determined and compared during a two-hour period which began two hours after injection of contrast medium. A strong degree of correlation was found between the elimination rates from serum and finger tissue and also between the total clearances calculated from the serum and finger measurements respectively. Thus, after radiographic examinations quantitative estimation of kidney function may be obtained as a fringe benefit by external X-ray fluorescence measurements of the elimination from tissue of the contrast medium used.			
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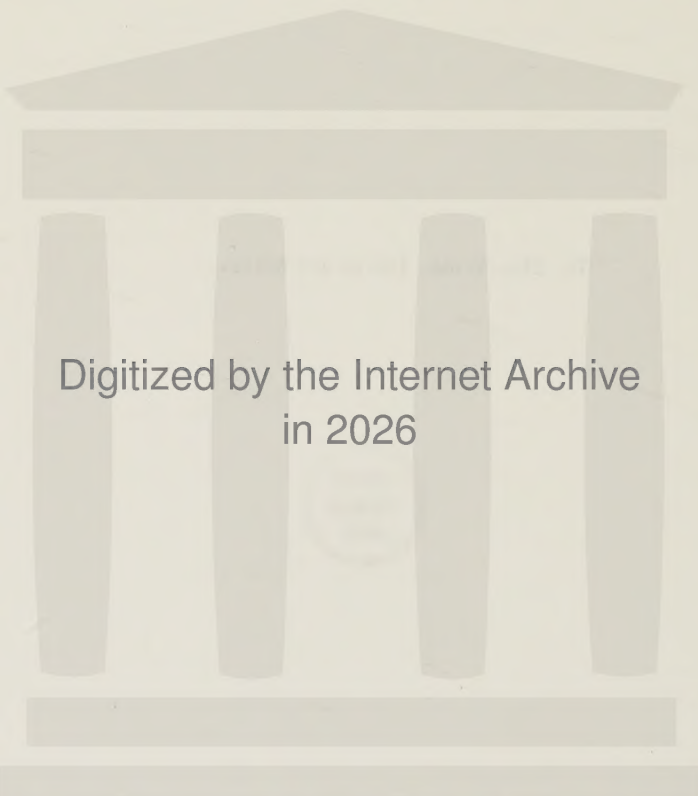
1981

IN VIVO X-RAY FLUORESCENCE ANALYSIS
FOR MEDICAL DIAGNOSIS

A new method for the non-invasive
determination of heavy metal levels
in biological samples with the use of
X-ray fluorescence spectroscopy.



To Elsa-Stina, Tobias and Niklas



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This thesis is based on the following papers, which in the text will be referred to by their Roman numerals.

I Grönberg T.

Optimization of non-invasive X-ray fluorescence measurements by means of Monte Carlo calculations.

Coden report: LUNFD6(NFRA-3026)/1-48/(1981)

II Grönberg T. and Mattsson S.

Monte Carlo determinations of optimal photon energies for XRF analysis of iodine in vivo.

Advances in X-ray analysis, 24, (000-000), 1981.

III Grönberg T., Almén T., Golman K., Lidén K., Mattsson S. and Sjöberg S.

Non-invasive estimation of kidney function by X-ray fluorescence analysis: Method for in vivo measurements of iodine containing contrast media in rabbits.

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IV Grönberg T., Sjöberg S., Golman K. and Mattsson S.

Non-invasive estimation of kidney function by X-ray fluorescence analysis: Elimination rate and clearance of contrast media in man.

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Svensk förening för nuklearmedicin, Malmö, 27-28 April, 1979.

Twenty-eight annual conference on applications of X-ray analysis, Denver, Colorado, USA, July 30-August 3, 1979.

Twenty-ninth annual conference on applications of X-ray analysis, Denver, Colorado, USA, August 4-8, 1980.

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1 INTRODUCTION

In 1913 Moseley discovered a well-ordered relationship between the X-ray energies and atomic numbers of elements and demonstrated that these X-rays - characteristic for the element - were a useful tool for both quantitative and qualitative chemical analysis.

This technique, - X-ray fluorescence analysis - was then considerably developed by de Broglie (1916) and Siegbahn et al. who extended Moseleys mapping of the elements (Siegbahn and Dolejšek 1922, Siegbahn and Thoraues 1924).

Quantitative measurements of the intensity relations of certain L X-ray lines were made by Jönsson (1927) and Eddy et al. (1929, 1930) who showed that it was possible to measure impurity concentrations in metal alloys of the order of $\mu\text{g/g}$.

In the late 1940's new interesting industrial applications were made and the technique of X-ray fluorescence analysis virtually recreated. These applications were at this time based on wavelength-dispersion spectrometers. The industrial applications demanded that many samples could be measured in a fairly short time. This made experimental calibration procedures with standard samples impractical and development of mathematical methods to convert fluence rate of characteristic X-rays to concentrations was started.

The main problem with the mathematical expressions created for this purpose was that they were more or less impossible to solve using the computers available at that time. Later progress in electronics, leading to relatively small high-speed computers has solved these problems.

With the development of compact radionuclide sources and semiconductor detectors with high energy-resolution such as Ge(Li)- Si(Li)- and later high purity Ge- detectors, medical in vivo application became a reality.

Pioneering work on the fluorescent scanning of naturally occurring iodine in the thyroid was carried out by Hoffer et al. (1968). This was possible because of the relatively

high iodine concentration in the thyroid ($\approx 400 \mu\text{g/g}$). In the same year 1968 Tinney (1968) published his work on theoretical (using analytical calculations) and experimental studies of the possibility of using X-ray fluorescence analysis to study organ structure and function. Several other authors have suggested the use of X-ray fluorescence analysis to follow in vivo the distribution and elimination of stable tracers which have been injected prior to the investigations. The technique permits measurements in a well defined volume and could be an alternative to studies with radioactive tracers. Experiments on animals have demonstrated its usefulness for measuring blood flow (Ter-Pogossian and Phelps 1971, Kaufman et al. 1978), cardiac output (Kaufman et al. 1972) and liver function (Koehler et al. 1976). The normal way here is to inject iodine containing contrast media and then follow variation in iodine concentration in the organ or tissue of interest with external measurements.

Lung function has been studied in dogs by in vivo measurements of the retention in the lungs of injected tantalum powder and/or barium containing contrast agents (Kaufman and Gamsu, 1974).

The possibilities for tomographic fluorescence scanning of injected bismuth (Bi-nitrate, Bi-citrate) preferentially taken up in brain tumours has also been proposed and studied in phantoms (Patton 1972). None of these methods has, however, as yet found any wide spread use as a clinical routine method for man.

To meet the growing demand for direct measurements of the concentration of various toxic substances in man, useful methods based on in vivo X-ray fluorescence analysis have been developed for lead (Ahlgren et al. 1976, Ahlgren and Mattsson 1979, Block et al. 1977) and cadmium (Ahlgren and Mattsson 1981).

2 IN VIVO APPLICATION OF THE X-RAY FLUORESCENCE TECHNIQUE

In the energy range considered in this work (approximately 20 - 150 keV), the interaction of photons with matter are due to:

(1) scattering by the atomic electrons with (incoherent-scattering) or without (coherent-scattering) loss of energy, or (2) by the photoelectric effect in which the photon transfers all its energy in the interaction.

When a well collimated beam of monoenergetic photons of energy $h\nu_0$ penetrate the body, there will be changes in their directional- and energy- distributions due mainly to incoherent scattering.

Scattered primary photons may reach the detector and thereby give rise to an interfering background distribution, which reduces the possibility of determining the amount of the trace element in question.

The normal situation is that the contribution from primary photons which have been incoherently scattered into the detector has higher energy than the characteristic X-ray photons.

In some situations it could, however, be possible to use an excitation energy $h\nu_0$ close to the K-edge of the trace element and to select the angle between incident and measured radiations so that the characteristic X-rays have higher energy than the incoherently scattered photons detected. An example of such a situation is the detection of lead ($\text{Pb } K_{\text{abs}}: 88.001 \text{ keV}$) using 88.035 keV photons from ^{109}Cd . This is however an exception.

In almost every situation the scatter contribution is a seriously limiting factor. It is especially troublesome in in vivo applications due to the large scattering volumes and the low concentration of the trace element.

If a (primary or scattered) photon of energy $h\nu$ penetrates soft tissue which contains a trace element, there is a certain possibility that the photon will interact by photoelectric absorption with an atom of the trace element. The

probability for this occurring is, in the actual concentration interval proportional to the concentration of the trace element and to the cross section for photoelectric absorption which is dependent on the energy of the photon and the atomic number of the element.

If $h\nu$ is greater than the electron binding energy B_k in the K-shell of the element of interest, absorption in this shell is favoured. The vacancy in the K-shell is filled by a transition from one of the outer shells, possible transitions being $L \rightarrow K$, $M \rightarrow K$ and $N \rightarrow K$.

In figure 1 are given schematically the transitions following a vacancy in the K-shell and the corresponding emission lines.

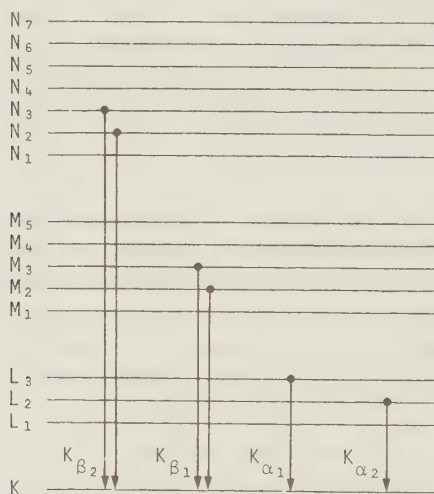


Fig 1. Schematic picture of the transition following a vacancy in the K-shell and spectrometric symbols of the corresponding emission lines.

The transition given in figure 1 may appear as characteristic X-rays with energy $h\nu_{ch} = B_k - B_s$ where B_s denotes the binding energy of one of the outer shells. The energy $h\nu_{ch}$ is characteristic of a certain element.

Alternatively, the reorganization may occur without emission of radiation. In this case, the energy is communicated to another electron (other electrons) of the same atom and this electron is ejected. This process is called the Auger effect.

The K-fluorescence yield, denoted ω_k , increases with the atomic number Z of the element, which favours in vivo detection of high Z -elements by means of the X-ray fluorescence technique.

In in vivo applications of X-ray fluorescence analysis the characteristic photons generated have to penetrate relatively thick layers of soft tissue, approximately 5 - 50 mm, in order to reach the detector.

This means that there is a lower limit to the emitted energy of the characteristic photons and hence to the atomic number of the element which is possible to measure.

An approximate lower limit of atomic number for an element to be measured in vivo is $Z = 30$ (Ahlgren 1980).

From this, it immediately follows that fluorescence following photoelectric absorption in soft tissue constituents does not interfere with the external detection of characteristic photons from the trace element.

In table 1 are given physical data for elements which are available for X-ray fluorescence measurements together with substances of medical interest which contain them.

Table 1

Elements administered to patients and available for non-invasive X-ray fluorescence measurements in vivo.

Element	Z	$E_{K_{abs}}$ keV	$E_{K_{\alpha 1}}$ keV	$E_{K_{\alpha 2}}$ keV	$E_{K_{\beta 1}}$ keV	$E_{K_{\beta 2}}$ keV	Substance of medical interest
Iodine	53	33.164	28.610	28.315	32.292	33.016	X-ray contrast agents
Barium	56	37.410	32.191	31.815	36.376	37.255	"
Platinum	78	78.379	66.820	65.111	75.736	77.866	"Cis-platinum" (cytostatic drug)
Germanium	32	11.103	9.885	9.854	10.985	11.100	"Spiro-germanium" (cytostatic drug)

3 AIM OF THE PRESENT INVESTIGATION

The aim of this work is 1) to make general theoretical studies of in vivo applications of X-ray fluorescence analysis by means of the Monte Carlo technique and 2) to investigate if an iodine containing X-ray contrast agent which is injected in urography could be routinely used for quantitative kidney function studies by in vivo measurements of the elimination of iodine in a peripheral well vascularized tissue.

Special emphasis is given to:

- Construction of a Monte Carlo code for use in a micro-computer
- Monte Carlo calculations of optimal conditions for X-ray fluorescence analysis in vivo

- quantitative estimation of the iodine concentration in the soft tissue of rabbits after intravenous injection of iodine-containing contrast media
- the relation of the elimination rate of the contrast agent as measured externally on the rabbit to the elimination rate as measured in vitro on serum samples drawn simultaneously with the external measurements
- studies of the possibility of using external X-ray fluorescence measurements for quantitative estimation of kidney function in man after injection of iodine containing contrast media (e.g. after urography).

4 MATERIAL AND METHODS

4.1 The Monte Carlo code

The Monte Carlo code (I) is constructed of several standard procedures and is a flexible and easy handled instrument suitable for use in a micro computer. A variance-reducing method known as "absorption by weight reduction" (Los Alamos, LA-7396M) has been applied so as to reduce the statistical uncertainty in the calculations of scatter spectra.

In order not to waste memory space, analytical expressions have been fitted to tabulated cross-section data, instead of storing these data as a matrix.

The program calculates (1) a quantity $P(I, E)$ which is proportional to the amount of K X-ray photons generated and (2) the energy distribution of the scattered photons I, E .

One assumption in the calculation of $P(I, E)$ is that the concentration of the trace element is so small that its presence has a negligible influence on the energy distribution of the exciting photons.

The P -value and the energy distribution of the scattered photons make it possible to obtain a relative estimate of the detectability of a trace element I, E .

4.2 Source, detectors and geometries used for the in vivo detection of iodine containing X-ray contrast media

To generate the emission of characteristic X-rays of iodine ($K_{\alpha} = 28.5$ keV) a dischaped ^{241}Am source of the activity 11 GBq has been used (III, IV). A source collimator of lead (III, IV) was used and in order to reduce the fluence of low energy photons from the source a 0.06 mm thick lead filter (III, IV) was placed in front of it.

The secondary radiation was studied using a 16 mm(diam) x 5 mm Ge(Li)-detector (III) or a Ge-detector (IV) of the same size connected via a pulsed optical feed-back preamplifier and a pulse shaping linear amplifier to a 80 MHz analog-to-digital converter. A base line restorer was used to maintain the energy resolution at the high countrates obtained (approximately 10^4 s^{-1} in the whole pulse height distribution). The collimator used in front of the detector was made of lead (III) or of high purity copper covered with high purity tantalum foils (IV).

The full energy peak efficiency and the total response function of the Ge-detector have been determined by means of published Monte Carlo calculated data and experiments performed in this work.

4.3 Measurements in rabbits (III)

Using the experimental set up discussed above one rabbit was used to determine the region of the body offering the best conditions for measuring iodine by means of external in vivo measurements.

Seventeen living rabbits were then used for estimation of the elimination rates of the contrast medium from their noses and from their blood. The measurement geometry is shown in paper III figure 1.

Nine of these rabbits were also measured externally after sacrifice and for calibration purposes, the soft parts of their noses were excised immediately after this measurement and about 2 g measured in vitro.

In the external measurements on the rabbit nose, the net countrates (a) of $I K_{\alpha}$ X-rays and (n) of 59.5 keV photons incoherently scattered at around 90° were measured. Count-rate (a) is proportional to the amount of iodine atoms in the irradiated volume seen by the detectors and (n) to the total mass in that volume.

To be able to correct for small changes in the amount of irradiated tissue the method was calibrated in terms of (a/n). The validity of this procedure was investigated using a dead rabbit (III). In this investigation the nose of the dead rabbit was moved in steps of 4 mm from the source (positive direction) and towards the source (negative direction). The measurement geometry may be studied in paper III, figure 1.

Serum samples were collected at 30 min intervals during the first 2 h and at 20 min intervals 2 - 4 h after the injection. The serum samples were measured in perspex test-tubes.

The elimination rates of the contrast agent as determined by external measurements on the noses of the living rabbits and by in vitro measurements on serum were compared.

4.4 Measurements in man

These measurements were carried out with the experimental set-up discussed in subsection 4.2.

Forty-four patients (IV) referred to the diagnostic X-ray department for urography and two healthy persons (III, IV, volunteered to take part in the investigation. The material thus consisted of 46 subjects; 11 women and 35 men. The patients had various urological and nephrological diseases.

After urography, external X-ray fluorescence analysis of iodine in the tip of the second finger of the left hand were made during 1 - 2 minutes at a time at 10 min inter-

vals during a 2 - 4 hours period. The reason for selecting the finger tip for these measurements is partly that the tip of the finger is well perfused and partly that it is very practical to measure there without inconvenience to the patient.

In the same way as in the measurements on rabbits (III), the quotient between the net countrate in the $I K_{\alpha}$ peak (a) and the countrate (n) in the compton distribution (a/n) was used so as to be able to correct for small changes in the amount of irradiated tissue. The validity of this correction has been studied (IV).

During the same period in which the external finger measurements were performed blood samples were drawn at 30 min intervals.

To be able to convert finger measurement data to iodine concentrations in serum, a conversion factor (denoted S) was determined. This conversion is necessary if we want to make a quantitative estimation of the kidney function, i.e., to determine clearance values. The elimination rates of the iodine-containing contrast medium as determined from finger and serum data have been compared as have corresponding clearance values for all the 46 patients.

To simplify calculations and to administrate the examination a micro-computer (ABC 80) was incorporated in the detector system (IV).

The absorbed dose and the energy imparted to the finger tip were measured by $3 \times 3 \times 1 \text{ mm}^3$ LiF-dosimeters. The results have been compared to the absorbed dose and the total energy imparted to patients during urography and also during a clearance determination with ^{51}Cr EDTA (III).

5 RESULTS AND DISCUSSION

5.1 Monte Carlo calculations

Considering the detection of iodine K_{α} photons (28.5 keV) the Monte Carlo calculations show that the main contribution from such primary photons (^{241}Am : 60 keV) which have been singly or multiply scattered in the phantom is well above the K_{α} energy (I).

However, when photons of this energy distribution reaches the detector we get a pulse height distribution which differs from the photon energy distribution. This pulse height distribution is a convolution of the photon energy distribution and the detector response function.

This means that, singly scattered photons at around 90° can be registered in the same part of the pulse height distribution as the K_{α} photons. This in turn means that we can reduce the background contribution in the energy interval of interest by reducing the number of single scattered photons at around 90° . This could be carried out e.g. by polarization of the primary photons.

Considering the detection of platinum K_{α} photons (66.2 keV) excited by 122 and 136 keV primary photons (^{57}Co) the scatter contribution are much more prominent in the total background distribution.

These facts have shown to be very little depending on the measurement geometry used (e.g., solid angle of detector and detector - collimator size).

However, the total background contribution in the energy intervals of interest (28.5 keV, 66.2 keV) increases with increasing solid angle of the detector and also with increased detector - collimator size. This increase is however not drastic (I).

The emission of characteristic X-rays is known to be isotropic. This means that the number of generated K_{α} photons

detected is proportional to the solid angle of the detector. It is thus easy to understand that a larger solid angle of the detector not only permits a larger trace element containing volume to be investigated but also increases the probability for every generated K_{α} photon to be detected (I).

The minimum detectable concentration of a stable tracer element using X-ray fluorescence analysis is proportional to $(\sqrt{b}/P)$, where b is the countrate in the background contribution and P is proportional to the number of detected K_{α} photons.

When the solid angle of the detector is increased the Monte Carlo calculations show that the detectability is improved. When the solid angle is kept constant considering the detection of K_{α} photons and the detector - collimator size is increased the detectability is slowly impaired.

In in vivo applications the size and position of a trace element distribution are often not well defined. Taking this into account the results in paper I show that it is better to use a large solid angle of the detector and a detector - collimator which ensures that the entire trace element distribution is seen by the detector. One might have expected that a narrow collimator at the detector would have been more advantageous due to reduction of the scatter contribution.

In paper II the optimal primary photon energy for in vivo detection of iodine has been estimated and found to be about 45 keV with no dependance on the depth of the distribution. The improvement compared to 60 keV (^{241}Am) was about 40%. The selection of primary photon energy is theoretically an important part of the optimization of the equipment. However, practical consequences must also be included in the detection. As stated in paper (II), it is doubtful whether a change from 60 keV photons (^{241}Am) to 45 keV photons obtained by using e.g. an X-ray tube with secondary target is justifiable considering the practical advantages of the ^{241}Am -source.

5.2 Measurements of the concentration and elimination of iodine-containing contrast media in rabbits and man.

The validity of using the Compton contribution (a_c) to correct for small changes in the rabbit measurement geometry (11) is examined in figure 1.

The basic assumption of this correction procedure is that the relative influence of irradiated iodine-containing and non-iodine containing tissue in the nose is unchanged when the rabbit moves its head.

Count rate ratio

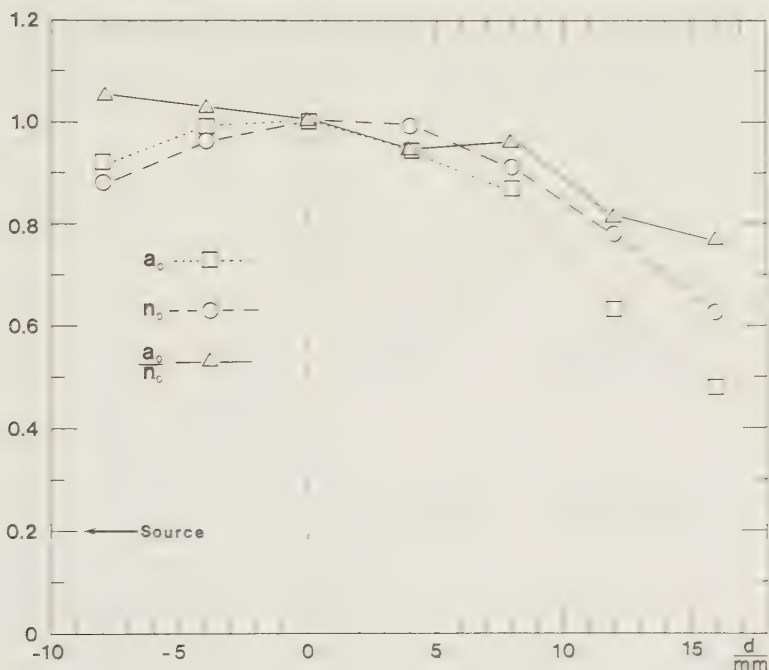


Fig. 1. Variation in the measured values of the net count rate in the K_{α} peak (a_0), the count rate in the Compton continuum (n_0) and in the ratio (a_0/n_0), with the position of the rabbit nose. Today I corrected that the values are normalized to $d = 0$.

From the figure it is obvious that this assumption is not entirely correct. However, the variation in the measured values of (a/n) , compared to the variation in the values of (a) , definitely justify the use of the correction procedure.

To illustrate the validity of this correction when measuring on the finger tip of humans (IV) two elimination curves from measurements of (a) and (a/n) are given in figure 3.

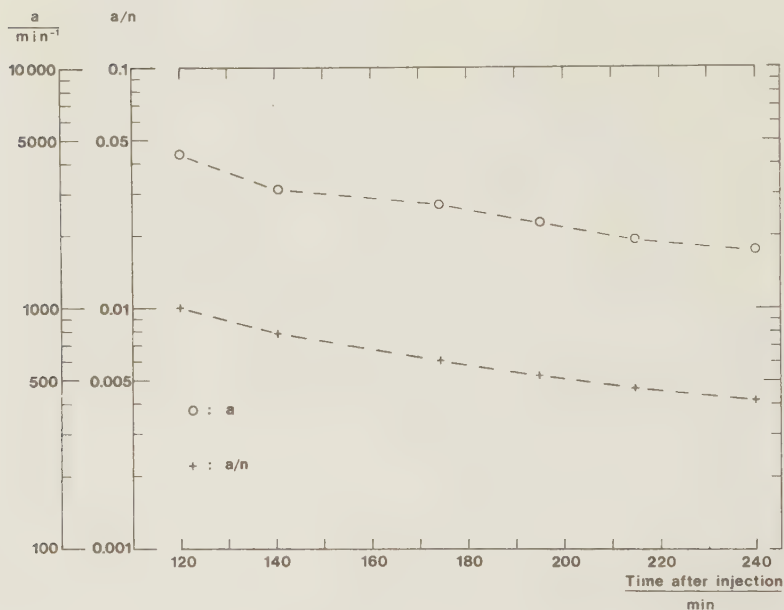


Fig 3. Elimination curves obtained from measurements of the net countrate in the $I K_{\alpha}$ peak (a) and the ratio between (a) and the countrate (n) in the compton distribution (a/n).

The correction procedure in this case is of course based on the same assumption as discussed above. From figure 3, it can be seen that the precision is improved when the ratio (a/n)

is used as a measure of the iodine content in the finger tip.

The elimination curves obtained by external in vivo measurements and in vitro measurements on serum samples are given for one rabbit in paper (III), (figure 2).

The curve obtained from external measurements on the rabbit nose is not normalized to the serum curve but represents true iodine concentration in nose tissue. The fact that the iodine concentration in the nose tissue was equal to that in serum was completely unexpected and is still unexplained. One would have expected a smaller amount of iodine per gram of nose tissue than per gram serum.

In paper IV (figure 3) are given the elimination curves for two healthy humans obtained from external in vivo measurements and in vitro measurements on serum samples. In this case the finger data are normalized to the serum curve.

A comparison between the figure 2 of paper III and figure 3 of paper IV gives that the form of the in vivo curves for rabbit nose and human finger tip differ considerably in the period 0 - 2 h after the injection.

This is, of course due to the fact that the tissue in the rabbit nose has different physiological properties than that in the human finger tip.

Approximately 2 h after injection, the elimination rates of the contrast medium as determined externally in vivo and the elimination rate as determined in vitro on serum samples are in good agreement in both cases.

This result is extremely important, since it is the elimination rate (β) of the substance from serum which can be related to kidney function. The correlation between the half life ($T_{1/2}$) of the contrast media as determined on rabbits externally and in serum samples are given in figure 3 in paper III ($T_{1/2} = (\ln 2)/\beta$). The correlation between the elimination rate of the contrast media as determined on humans externally and on serum samples are given in figure 4 in paper IV.

A schematical explanation of the elimination curve profiles and of the correlation between the elimination rates obtained in vivo and in vitro is given in paper IV pages 11 - 12.

The estimation of absolute values of the kidney function after injection of iodine containing contrast medium, in terms of clearance (Cl) is discussed in paper IV .

The correlation between clearance values obtained from the external in vivo measurements and from in vitro measurements on serum samples is given in figure 6 in paper IV.

The absorbed dose and the energy imparted which is given to the patients in the external measurements on humans, are presented in paper III. The energy imparted is estimated to be 0.003 mJ which is quite negligible compared to that of urography.

6 CONCLUSION

The Monte Carlo program constructed in this work (I) together with a knowledge of the Ge-detector response function (I) has shown to be valuable tools in order to make theoretical studies of in vivo applications of the X-ray fluorescence technique (I, II).

The results given in paper I and II should be considered as the start of a more detailed study of various parameters influencing the in vivo measurements. The practical consequences of such theoretical studies could be development of more efficient measurement equipment for different in vivo applications.

The studies of the elimination of iodine-containing contrast media from rabbits and from humans show that it is possible to estimate the elimination rate of these substances in serum from external measurements on peripheral tissue such as a rabbit nose and on a human finger tip.

The practical consequences of the studies on rabbits are that the in vivo measurements could now be used e.g. in tests of new contrast media. The method could also be used for animal tests of new drugs with suspected influence on kidney function, with the iodine containing contrast medium as tracer.

The practical consequence of the results obtained from measurements on humans is that external measurements on the finger tip can be used routinely for quantitative estimation of the kidney function, on patients referred for urography. The method developed in this work (IV) is simple to handle with no inconvenience to the patients.

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OPTIMIZATION OF NON-INVASIVE X-RAY FLUORESCENCE MEASUREMENTS BY
MEANS OF MONTE CARLO CALCULATIONS

Theoretical and experimental investigations of some representative geometries in clinical use for determination of an iodine-containing contrast agent or platinum-containing cytostatic agent

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Theoretical and experimental investigations of some representative geometries in clinical use for determination of an iodine-containing contrast agent or platinum-containing cytostatic agent.

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A Monte Carlo code has been used to simulate the scatter spectra obtained in various in vivo X-ray fluorescence measurements. The structure of the scatter spectra has been investigated and discussed. Studies of the response function of the Ge-detector used have made it possible to convert the calculated scatter spectra to pulse-height distributions. The Monte Carlo programme also calculates a parameter (denoted P) which is under certain conditions proportional to the amounts of characteristic photons generated from some trace-element. The calculated pulse-height distributions and P values have been used to study the influence of detector geometry on the relative detectability of iodine and platinum. The Monte Carlo code and a thorough knowledge of the Ge-detector response function have shown to be valuable tools in designing X-ray fluorescence equipment.

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1 INTRODUCTION

When the X-ray fluorescence technique is used for external in vivo measurements, the experimental set-up has very often to be changed from one application to the next, and many variable parameters are involved. Examples of such parameters are: primary photon energy, source, source-collimation, detector and detector-collimation.

There is obviously need for a theoretical model to estimate optimal conditions for a particular application. The Monte Carlo technique is of great use in practical applications involving particle-transport problems of this type, while analytical solutions are by their nature often very complicated.

The X-ray fluorescence system used in in vivo applications presented here consists of monoenergetic sources of radioisotopes such as ^{241}Am and ^{57}Co , a high-purity Ge-detector and a multichannel analyzer. In this system, we have incorporated a micro-computer (ABC 80) which is normally used for the administration of in vivo measurements and to perform some of the calculations.

This computer is programmed in BASIC which makes it rather slow. However, since the availability of the computer is extremely good we considered it advantageous to use it in developing the Monte Carlo code.

The algorithms used in the programme are presented in section 2. Since a large number of questions are taken up in this work, the results and discussions are given directly following the presentation of each particular topic in question. The reader is assumed to be familiar with the basic features of the X-ray fluorescence technique.

The purpose of the present work is:

- To develop an easily-handled and fairly efficient code for optimization purposes, this to be used in a micro-computer already incorporated in the X-ray fluorescence system.
- To verify experimentally the validity of the simulated approximative geometry.
- To estimate the Ge-detector response function, by means of experiments and published data.
- To study the influence of method of sampling the Klein-Nishina function on the calculated scatter spectra.
- To calculate the energy distribution of primary photons which reach the detector after being scattered in the phantom.
- To compare calculated scatter spectra converted to pulse-height distribution with experimentally obtained pulse-height distributions.
- To calculate the influence of different source and detector geo-

metries on the numbers of iodine and platinum K_{α} -photons generated and detected.

—— To calculate the influence of various detector geometries on the background in the energy intervals of interest and their influence on the minimum detectable concentration.

2 PRINCIPLES OF THE MONTE CARLO CODE

2.1 Simulated experimental set-up

One possible experimental situation is measurement on a small volume of the kidney, where the analysis of such stable tracers, as iodine-containing contrast agents and platinum from chemotherapeutic media, are of interest for analysis in patients. In figure 1 is shown schematically a two-dimensional representation of such an in vivo situation with the so-called 'region of interest' with regard to both the scatter contribution and characteristic X-rays emitted, defined by the dotted lines. Three-dimensionally, I have assumed that the region of interest could be described as a cylinder and the volume containing the trace-element as a sphere. This assumption may be applied in many similar in vivo applications.

In figure 2 the geometry simulated by the computer is shown. The cylindrical phantom is described mathematically by

$$x^2 + z^2 \leq R_1^2 \quad y \geq -l_1 \quad 2.1.1$$

Here, R_1 denotes the radius of the cylinder and l_1 the distance from the origin of the coordinate system to the position of the source collimator. The centre of the sphere V containing the trace-element defines the origin in the coordinate system and the sphere itself is described mathematically by

$$x^2 + y^2 + z^2 \leq R_2^2 \quad 2.1.2$$

Here, R_2 denotes the radius of sphere V . The distance d_1 given in figure 2 represents the track-length in the sphere V of a photon crossing it. The source-collimator of radius R_3 is defined by

$$x^2 + z^2 \leq R_3^2 \quad y = -l_1 \quad 2.1.3$$

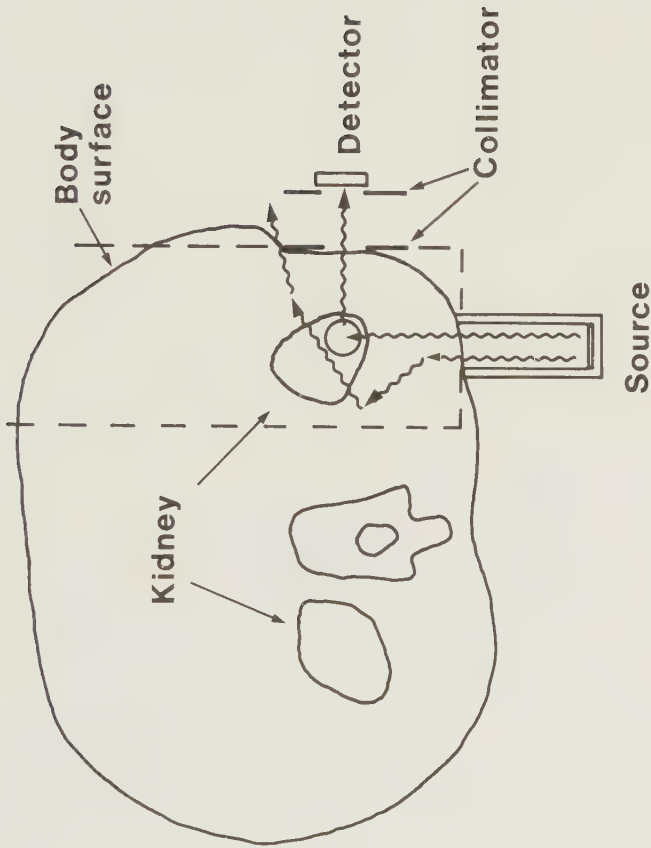


Fig. 1 Schematic experimental set-up for XRF-analysis of a trace element in the right kidney.

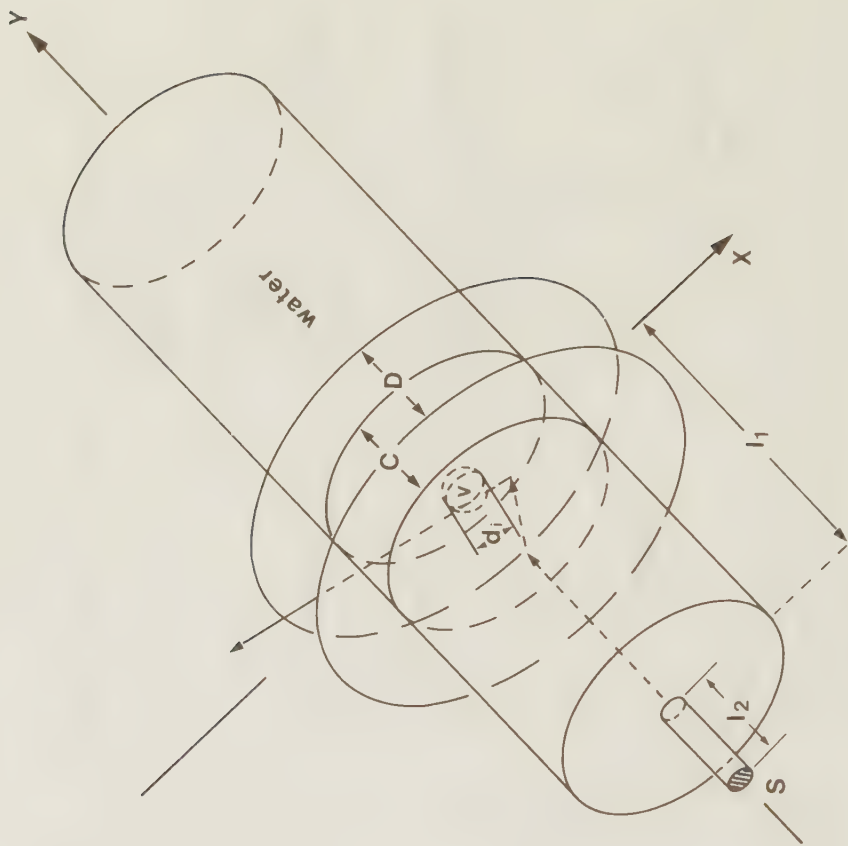


Fig. 2 Set-up used for simulation of in vivo XRF-measurements, where S denotes source, l_2 =distance between source and phantom, l_1 =depth of the trace element containing sphere V, C denotes detector-collimator and D the detector, d_1 is track-length of a photon in the sphere V.

The disc-shaped source S with radius R_4 at a distance l_2 from its collimator is defined by

$$x^2 + z^2 \leq R_4^2 \quad y = - (l_1 + l_2) \quad 2.1.4$$

To reduce the number of rejected scattered photons (i.e., photons escaping the cylinder without being registered), a cylindrical detector system is used in the simulations (see figure 2).

The detector-collimator, positioned at distance R_1 (radius of cylinder), from the origin is defined by

$$x^2 + z^2 \leq R_1^2 \quad -\frac{C}{2} \leq y \leq \frac{C}{2} \quad 2.1.5$$

where C is the collimator width.

The detector positioned at distance R_5 from the origin is defined by

$$x^2 + z^2 \leq R_5^2 \quad -\frac{D}{2} \leq y \leq \frac{D}{2} \quad 2.1.6$$

where D represents the detector width.

Note: Throughout this work, we have used the pseudo-random numbers ξ , (where $\xi_1, \xi_2, \dots$ are independent random numbers), generated by an assembler routine in the computer. These numbers are assumed to be uniformly distributed in the interval $]0,1[$.

For a continuous stochastic variable v with probability-density function $f(v)$ and probability-distribution function $F(v) = \int_{-\infty}^v f(v)dv$, it can be shown generally that by putting $v = F^{-1}(\xi)$, the available uniformly-distributed variable ξ is transformed into the desired variable v . In the following text, this is referred to as the "basic principle" (1).

2.2 Source photons

Determination of starting-points

In order to simulate a photon history, the first step is to determine the starting-point of the photon in the source, using the available uniformly distributed random numbers ξ .

The starting-point of a photon from the source is a two-dimensional stochastic variable uniformly distributed on the disc, defined in polar coordinates (R_S, ϕ_S) by $R_S \leq R_4$ and $-\pi < \phi_S \leq \pi$, (see figure 3).

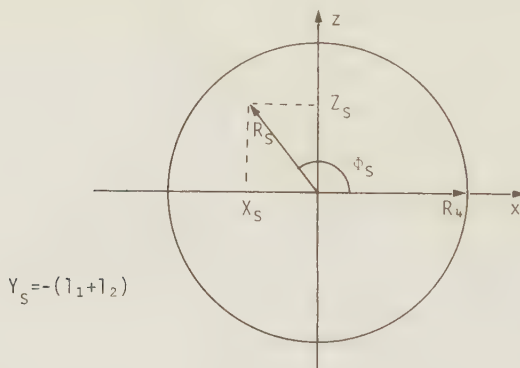


Figure 3 Schematic drawing of the simulated source

The probability density $P(R_S, \phi_S)$ for the point of emission is

$$P(R_S, \phi_S) = P(R_S) \cdot P(\phi_S) = \begin{cases} \frac{2 \cdot R_S}{R_4^2} \cdot \frac{1}{2\pi} & R_S \leq R_4 \\ 0 & R_S > R_4 \end{cases}$$

Since the probability density can be factorized, R_S and ϕ_S are independent variables. The "basic principle" gives

$$\phi_S = \pi(2\xi_1 - 1) \quad 2.2.1$$

$$R_S = R_4 \cdot \sqrt{\xi_2} \quad 2.2.2$$

The starting-point in Cartesian coordinates is now given by

$$X_S = R_S \cdot \cos(\phi_S)$$

$$Y_S = -(l_1 + l_2) \quad 2.2.3$$

$$Z_S = R_S \cdot \sin(\phi_S)$$

Direction of the source photons

The next step is to determine the direction of an emitted photon. The probability for emission through the collimator opening for each photon generated is $\Omega_S/4\pi$, where Ω_S is the solid angle of the collimator-opening, as seen from the starting-point of that photon. In this work, complete directional biasing of the source photons is made. This means that all the source photons are assumed to penetrate the cylindrical water phantom. The simulated geometry is such that Ω_S may be considered constant across the source and the photon fluence across the collimator opening may be approximated by a constant. These approximations make it simple to determine the direction of the source photons.

(1) A uniformly-distributed point $(X_C, -l_1, Z_C)$ in the collimator opening is selected according to the method discussed above. The photon starting at $(X_S, -(l_1 + l_2), Z_S)$ is assumed to pass through the collimator at this point.

(2) The direction cosines x , z and y are then given by

$$x = (X_C - X_S) / l_2$$

$$z = (Z_C - Z_S) / l_2 \quad 2.2.4$$

$$y = \sqrt{1 - x^2 - z^2}$$

To be able to compare results for different source-geometries, it is necessary to relate the numbers of photons passing through the source to the "true" number of photons emitted from the source, the source strength. The source geometries used makes it reasonable to assume that the collimator angle Ω_S is a constant for all points in the source approximated by the value for the centre of the source.

This approximation makes it possible to use $\Omega_S/4\pi$ as a weighting factor for the source photons, and thus be able to compare different source geometries.

2.3 Physical data

Tabulated cross sections

In particle transport simulation with the Monte Carlo method, cross section data are needed. To be able to sample the pathlength between two interactions for the random walk in the water phantom, we need the total attenuation coefficient μ_w . We also need information on the cross section for scattering σ_w in order to sample the interaction mode.

Once an interaction point has been determined, we consider the interaction to be either Compton scattering or photoelectric absorption, thus excluding coherent scattering in order to simplify the calculations. In spite of this, σ_w and hence μ_w include coherent scattering since otherwise we would overestimate the mean free paths of the photons and also the probability for photoelectric absorption. In the present work, we have made a comparison of the total attenuation coefficient μ_w in the energy interval 20-150 keV, from seven different sets of tabulated value (2,3,4,5,6,7,8) with the values shown in table 1.

According to HUBBELL (1969), the uncertainty in the attenuation data for low Z materials such as water is about 1% in the energy interval 30 keV to 100 MeV, but below 30 keV this uncertainty might increase to 5 - 10%. This increase is due to 1) poor knowledge of the photoeffect for low Z materials, 2) corrections to experiments due to high Z impurities and 3) departures of the Compton scattering cross sections from the values calculated using Klein-Nishina theory.

From table 1, it can clearly be seen that the agreement between the results of different authors improves when the energy increases, which confirms the discussion above.

Finally, in order to determine the amount of characteristic X-rays generated, we require the cross sections for photoelectric absorption, τ , of the trace element in question.

Similarly as for μ_w , we have made a comparison of τ_I and τ_{Pt} as given in four different tabulations (2,4,6,8) and the results are presented in table 2. According to HUBBELL (1969), the uncertainties in cross section data for such high Z material as iodine and platinum are about 1 - 2% far from an edge, increasing to 5 - 10% close to absorption edges.

According to STORM and ISRAEL (1970), their results of calculations of the photo absorption coefficients for high Z materials tend to be within 3% both of other calculations and measurements in the energy interval 6-200 keV.

Table 1 Total mass attenuation coefficient (μ/ρ {cm²/g}), in water (H₂O), as given in seven different tables.
In the last column is given the relative range defined as $\frac{\mu_{\max} - \mu_{\min}}{\mu} \cdot 100$

Energy keV	Hubbell NBS 1969 (TE)	ICRU 17 1970 (TE)	Storm-Israel Nuclear Data 1970 (T)	Hubbell Atomic Data 1971 (E)	Viegele Atomic Data 1973 (TE)	Hubbell Radiation Res. 1973 (TE)	Plechaty UCRL-50400,6 1978 (T)	Relative range
20	0.775	0.773	0.790	0.750	0.809	0.7956	0.7608	7.6
30	0.370	0.364	0.371	0.382	0.377	0.3716	0.3610	4.9
40	0.267	0.264	0.267	0.276	0.270	0.2668	0.2627	4.5
50	0.227	0.225	0.226	0.236	0.228	0.2262	0.2243	5.1
60	0.206	0.205	0.205	0.215	0.206	0.2055	0.2045	5.1
80	0.184	0.183	0.183	0.187	0.184	0.1835	0.1832	2.2
100	0.171	0.171	0.171	0.167	0.171	0.1707	0.1705	2.4
150	0.151	0.150	0.150	0.149	0.151	0.1505	0.1504	1.3

E: Experimentally obtained values

T: Theoretically " "

Table 2 Cross section for photo-electric absorption (τ {b/atom}) of ^{53}I and ^{78}Pt as given in four different tables

Energy keV	Hubbell NBS 1969 (TE)		Storm-Israel Nuclear Data 1970 (T)		Viegele Atomic Data 1973 (TE)		Plechaty UCRL-50400, 6 1978 (T)	
	I	Pt	I	Pt	I	Pt	I	Pt
33.17	7520	-	7410		8090		7432	
40	4660	-	4510		4820		4597	
50	2570	-	2480		2580		2544	
60	1560	-	1510		1540		1548	
78.40		-		2840		3140		2872
80	714	-	676	2730	678	2960	695	2720
100	377	-	359	1520	357	1560	369	1492
150	118	-	113	522	111	505	116	497

E: Experimentally obtained values

T: Theoretically " "

Analytical expressions for cross section data

In a large computer, it is very convenient to have the cross section data available in matrix form and to interpolate between the different values. In our micro-computer, this is possible over selected ranges of energy, but is still a waste of the limited memory capacity. We have instead chosen to fit simple analytical expressions to the tabulated cross section data. The results of the discussion above give the limits of uncertainty for the values calculated by the following analytical expressions for cross section data. We made the assumption that in the energy interval 20–150 keV the data of interest could be expressed in the form $a \cdot (h\nu)^b + c$, where a , b and c are constants.

The expression fitted to the tabulated values of the attenuation coefficient $\mu_w(2)$ is

$$\mu_w(h\nu) = 473.9 (h\nu)^{-2.21} + 0.144 \quad 2.3.1$$

$$20 \leq h\nu \leq 150 \text{ keV}$$

In figure 4 are shown the tabulated μ_w -values and the curve obtained from equation 2.3.1.

The analytical expression fitted to the tabulated values of $\sigma_w(2)$ is:

$$\sigma_w = 0.9456 \cdot (h\nu)^{-0.558} + 0.092 \quad 2.3.2$$

$$20 \leq h\nu \leq 150 \text{ keV}$$

The tabulated values of σ_w are shown in figure 5 together with the curve obtained from the analytical expression.

To be able to sample the interaction mode, we need information on the quotient $(\sigma/\mu)_w$. In the energy interval $[20, 63.6]$ keV, $(\sigma/\mu)_w$ can be derived from the quotient of equations 2.3.2 and 2.3.1 but in the energy interval $[63.6, 150]$ keV, it is preferable to use the expression 2.3.3, because of minor imperfections in the analytical expressions 2.3.2 and 2.3.1.

$$(\sigma/\mu)_w = 3.33 \cdot 10^{-4} \cdot (h\nu)^{-1} + 0.94 \quad 2.2.3$$

$$63.6 < h\nu \leq 150 \text{ keV}$$

In figure 6 is shown the quotient of $(\sigma/\mu)_w$ as calculated from the tabulated values and the curves obtained from the analytical expressions.

Attenuation coefficient, μ_w

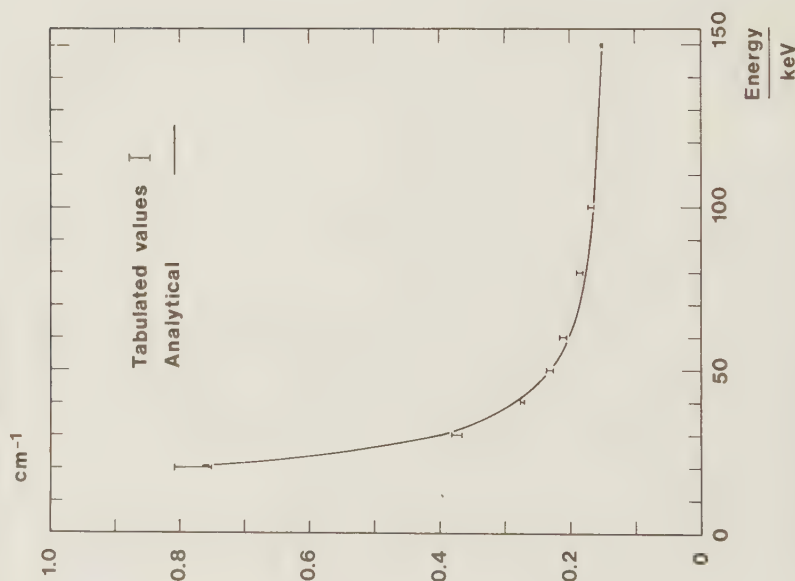


Fig. 4 Range of tabulated total attenuation coefficients for water at various photon energies and the curve fitted to these data (eq. 2.3.1)

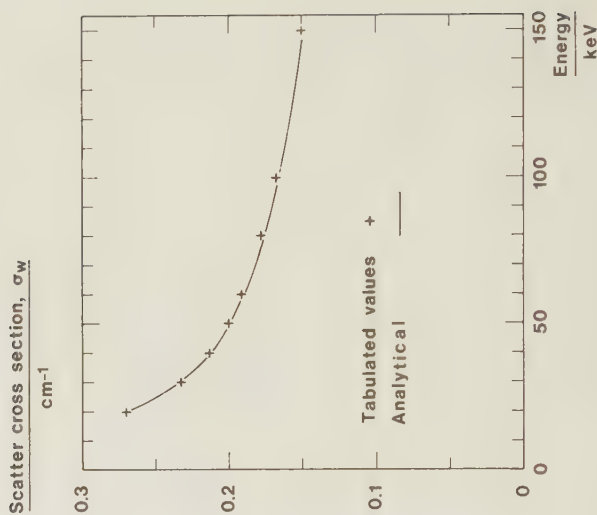


Fig. 5 The total scatter cross section for scattering in water as given in the tabulations and the curve fitted to these data (eq. 2.3.2).

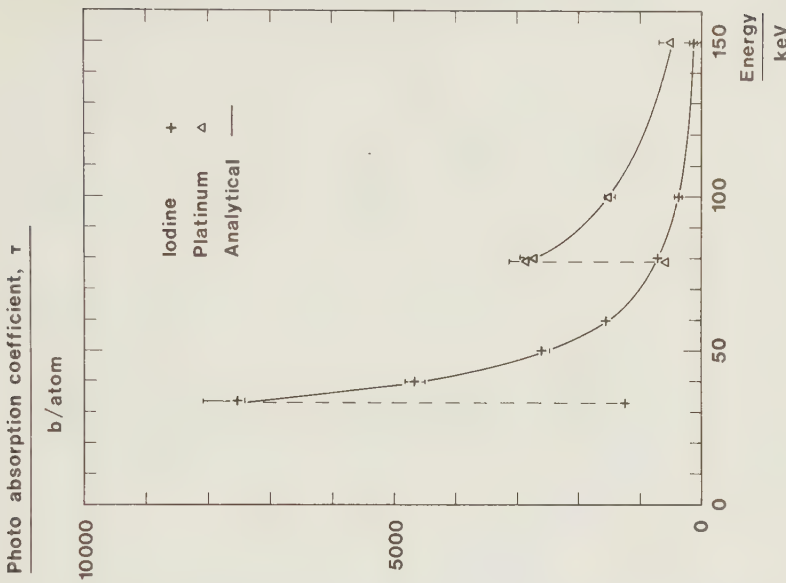


Fig. 7 The cross sections for photo-electric absorption for iodine and platinum as given in the tabulations together with the curves fitted to these data.

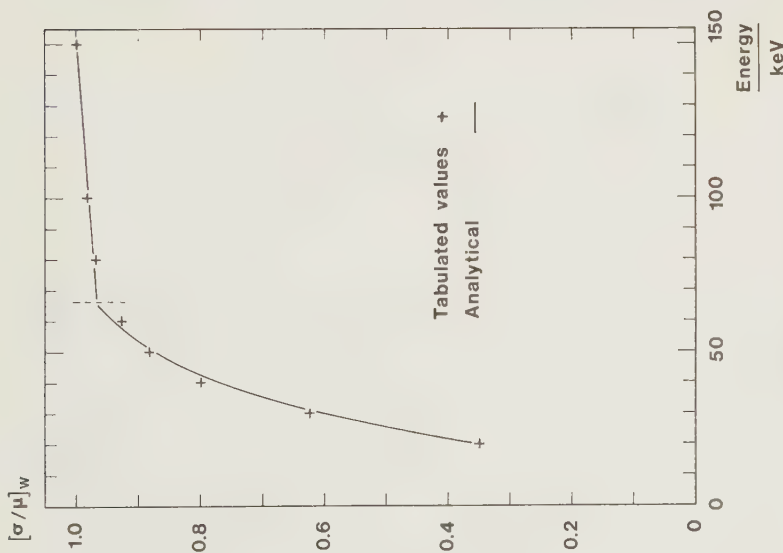


Fig. 6 Ratio between total scatter cross section and total attenuation coefficient (Hubbell 1969) and the curve fitted to these data.

In equation 2.3.4 is given the expression fitted to the tabulated values of τ_I , (2) and in equation 2.3.5 is given the expression fitted to the values of τ_{Pt} (4).

$$\tau_I = 8.0 \cdot 10^7 (h\nu)^{-2.647-21} \quad 2.3.4$$

$$33.2 \leq h\nu \leq 150 \text{ keV}$$

$$\tau_{Pt} = 2.59 \cdot 10^8 \cdot (h\nu)^{-2.615-5.14} \quad 2.3.5$$

$$78.4 \leq h\nu \leq 150$$

The curves obtained from these expressions are given in figure 7 together with the tabulated values.

From the results presented in figure 4 - 7, one may conclude that the analytical expressions stay within the limits of uncertainty of the corresponding published data.

2.4 Determination of track-length

The track-length s of a photon in a medium is exponentially distributed in the interval $s > 0$ with probability density function $f(s) = \mu \cdot e^{-\mu \cdot s}$, where μ is the total attenuation coefficient for the medium in question, in this work water (μ_W). The "basic principle" gives

$$s = -\frac{1}{\mu_W} \cdot \ln \xi_3 \quad 2.4.1$$

representing the track-length of the photon in the water phantom.

2.5 Registration of photon flight

The photon track between two points of interaction ($X_{n-1}, Y_{n-1}, Z_{n-1}$) and (X_n, Y_n, Z_n) is a straight line. Introducing the parameter t , this track is expressed by

$$\begin{aligned} X &= X_{n-1} + (X_n - X_{n-1}) \cdot t \\ Y &= Y_{n-1} + (Y_n - Y_{n-1}) \cdot t \\ Z &= Z_{n-1} + (Z_n - Z_{n-1}) \cdot t \end{aligned} \quad 0 \leq t \leq 1 \quad 2.5.1$$

Of interest in this work is to determine whether or not the photon has in some way crossed sphere V containing the trace element.

The surface of this sphere is given by

$$x^2 + y^2 + z^2 = R_2^2 \quad 2.1.2 \text{ a}$$

We have thus to solve the following equation for t , derived by inserting equation 2.5.1 in equation 2.1.2 a.

$$\begin{aligned} & \{X_{n-1} + (X_n - X_{n-1}) \cdot t\}^2 + \{Y_{n-1} + (Y_n - Y_{n-1}) \cdot t\}^2 + \{Z_{n-1} + (Z_n - Z_{n-1}) \cdot t\}^2 = \\ & = R_2^2 \end{aligned} \quad 2.5.2$$

If the solution is real and if at least one of the roots t_1 , t_2 is in the interval $[0, 1]$, the photon has crossed or penetrated the sphere. A further analysis of t_1 and t_2 yields the possibility of calculating d_i , (the track-length in sphere V).

If the photon has escaped the cylinder, then we want to know if the escape has been through the collimator and detector. The procedure in this case is similar to that one described above.

The X' and Z' coordinates for the intersection with the shell of the cylinder are determined by inserting

$$\{X_{n-1} + (X_n - X_{n-1}) \cdot t\} \text{ and } \{Z_{n-1} + (Z_n - Z_{n-1}) \cdot t\}$$

in equation 2.1.1 a describing the shell of the cylinder

$$x^2 + z^2 = R_1^2 \quad 2.1.1 \text{ a}$$

Thus we have to solve the following equation for t

$$\{X_{n-1} + (X_n - X_{n-1}) \cdot t\}^2 + \{Z_{n-1} + (Z_n - Z_{n-1}) \cdot t\}^2 = R_1^2 \quad 2.5.3$$

That one of the solutions t_1 or t_2 which lies in the interval $[0, 1]$ gives the corresponding Y' value.

If the following relation is satisfied we know that the photon has escaped through the collimator

$$|Y'| \leq \frac{C}{2} \quad 2.5.4$$

The same procedure is used to determine whether or not the photon has also passed through the detector.

2.6 Methods of sampling the Klein-Nishina function

The differential cross section and the photon energy distribution

According to the Klein-Nishina formula, the differential cross section $\sigma_E(\Omega)$ {cm²/ steradian} is given by:

$$\sigma_E(\Omega)d\Omega = \left(\frac{r_0^2}{2}\right) \cdot \frac{1+a^2}{\{1+E(1-a)\}^2} \left[1 + \frac{E^2(1-a)^2}{(1+a^2)\{1+E(1-a)\}}\right] d\Omega \quad 2.6.1$$

Here, $r_0 = \frac{e^2}{m_0 c^2} = 0.28183 \cdot 10^{-12}$ cm, $E = \frac{h\nu}{m_0 c^2}$ and $a = \cos \theta$, where θ

denotes the compton scattering angle and $h\nu$ is the energy of the incident photon.

The relation between the energy of the scattered photon E' and (E, a) is:

$$E' = \left\{ \frac{E}{1+E(1-a)} \right\} \quad 2.6.2$$

Using the relation $d\Omega = 2\pi \sin \theta \cdot d\theta$, we may express the differential cross section as:

$$\sigma_E(E')dE' = \sigma_E(\Omega)d\Omega = \sigma_E(\Omega) 2\pi \sin \theta d\theta \quad 2.6.3$$

The next step is to rewrite 2.6.2 in the form

$$a = 1 + \frac{1}{E} - \frac{1}{E'} \quad 2.6.4$$

Since $a = \cos \theta$, it follows that $da = -\sin \theta d\theta$, which means that $\sigma_E(E')dE' = -\sigma_E(\Omega) \cdot 2\pi(da)$.

Using this expression and equations 2.6.1 and 2.6.4, we obtain the following result:

$$\sigma_E(E') = \pi r_0^2 \cdot \left(\frac{E'}{E}\right)^2 \cdot \left\{ \frac{E'}{E} + \left(\frac{2}{E} + \frac{1}{E^2}\right) + \left(E - \frac{2}{E} - 2\right) \cdot \left(\frac{1}{E'}\right) + \left(\frac{1}{E'}\right)^2 \right\} \quad 2.6.5$$

Various methods have been used to sample the compton scattering angle θ from the Klein-Nishina function expressed in 2.6.5.

As early as 1956, Kahn (9) devised a rejection technique to sample the scattering angle. This rejection technique is thoroughly described in refs 10 and 11. Another method which has been widely used is to approximate the inverse function ("basic principle") (12). The computational speeds and accuracies of these two methods, which are both recommended in ref 10, have been compared in this work.

Comparison of the rejection technique and the approximation to the inverse of the function

The average computational time for the rejection technique (10) has in this work been determined to be about 0.16 seconds. The corresponding time used in the routine constructed for the inverse function approximation (12) in which every random number leads to a scattering angle is 0.07 seconds. The rejection technique is thus a factor of 2.3 slower than the inverse function method. In figure 8 is shown the distribution of θ for $h\nu=20$ and 150 keV, as determined by the rejection technique, and the corresponding curves obtained analytically from equation 2.6.5 and 2.6.4. Agreement is seen to be good. The statistical uncertainty in the sampled values is about 3 - 4%.

In figure 9 is plotted the distribution of θ for $h\nu=20$ and 150 keV, as determined by the inverse function approximation and the corresponding curves obtained from equation 2.6.5 and 2.6.4.

As can be seen from figure 9, there is rather poor agreement between the sampled values and the curves obtained from equation 2.6.5. This particular approximation to the inverse function clearly underestimates the probability of scattering in the backward direction. The influence of this lack of agreement on the scatter spectra calculated by Monte Carlo methods is discussed in subsection 6.

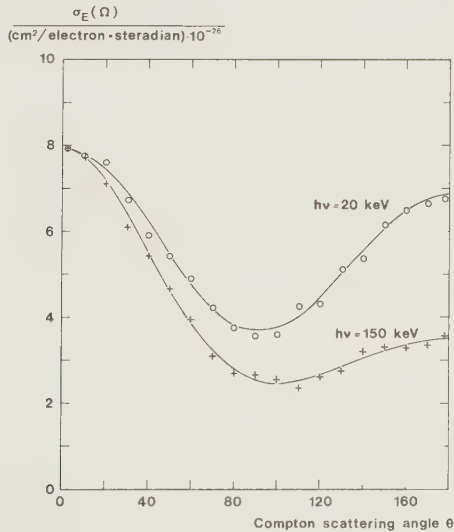


Fig. 8 The distribution of the compton scattering angle as calculated analytically (solid curves) and as sampled by the rejection technique.

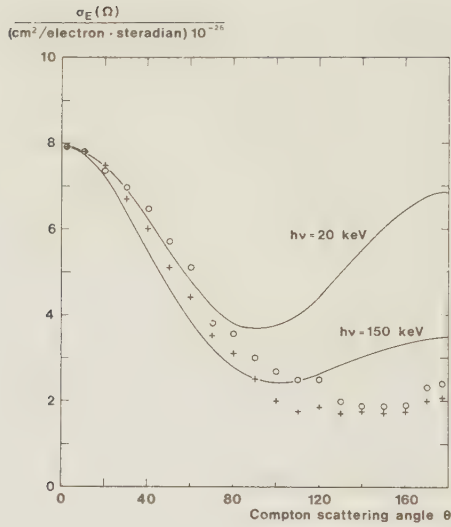


Fig. 9 The distribution of the Compton scattering angle as calculated analytically and as sampled by the inverse function method.

2.7 Photon direction after collision

When the value of the scatter cosine $a = \cos\theta$ is selected, we have to calculate new direction cosines according to the following, where α denotes the rotational angle:

$$\left\{ \begin{array}{ll} a_1 = a = \cos\theta & ; \quad 0 \leq \theta \leq \pi \\ a_2 = 1 - a_1^2 & \\ a_3 = \cos\alpha & ; \quad \alpha = \pi (2\xi_1 - 1) \\ & \\ & - \sqrt{1 - a_3^2} & ; \quad \alpha \leq 0 \\ a_4 = & + \sqrt{1 - a_3^2} & ; \quad \alpha > 0 \end{array} \right. \quad 2.7.1$$

If the original direction cosines are x, y, z , the new ones may be written as

$$\begin{aligned}x' &= (a_2 \cdot a_3 \cdot z \cdot x - a_2 \cdot a_3 \cdot y) / \sqrt{1 - z^2} + a_1 \cdot x \\y' &= (a_2 \cdot a_3 \cdot z \cdot y - a_2 \cdot a_3 \cdot x) / \sqrt{1 - z^2} + a_1 \cdot y \\z' &= -a_2 \cdot a_3 \cdot \sqrt{1 - z^2} + a_1 \cdot z\end{aligned}\quad 2.7.2$$

However, if the absolute value of z is too close to unity, it is better not to take the rotation into account but instead to use the following formulae to determine x', y' and z'

$$\begin{aligned}x' &= a_2 \cdot a_3 \\y' &= a_2 \cdot a_4 \\z' &= a_1 \cdot z\end{aligned}\quad 2.7.3$$

A complete derivation of the expressions given in this section can be found, e.g., in ref 12.

2.8 Absorption by weight reduction

Analogue sampling very often requires long running times to determine some quantity of interest with acceptable precision. To avoid such long running times, one or a couple of schemes to alter or bias the probability density function could be applied.

To improve the statistics in the low-energy part of the scatter spectrum, we have used a variance-reducing method called "absorption by weight reduction" (13). Absorption may be treated in two ways, 1) explicit analogue absorption in which the photon is absorbed and its track terminated or 2) implicitly by reducing the photons' weight according to the scattering probability and then allowing it to proceed. The weight of the photon after n interactions is given by:

$$w_n = w_{n-1} \cdot \frac{\sigma(h_{n-1})}{\mu(h_{n-1})}\quad 2.8.1$$

Here σ denotes the Compton scattering cross section and μ the total attenuation coefficient.

2.9 Characteristic X-rays and scatter spectra

Characteristic X-rays

Since the trace elements in medical applications are present only in very small concentrations, it would be impractical to calculate the absolute number of characteristic X-rays generated. Instead, I have defined a parameter P which is proportional to this number.

$$P = \{ \Sigma \tau_i(h\nu) \cdot (d_i/d_{\max}) \cdot W_i \} / N_0 \quad 2.9.1$$

Here, N_0 is the number of primary photons generated in the source, d_i the track-length in the sphere V, $d_{\max} = 2 \cdot R_2$ is the diameter of the sphere and τ_i is the cross section for photo-electric absorption in the trace element in question. Since τ_i has dimension {barn/atom}, P will be given in {(barn/atom) / generated source photon}. If the trace element concentration is considered to be less than 100 $\mu\text{g/g}$ water, the total attenuation coefficient in the sphere V will be increased by less than 5% compared to the total attenuation coefficient for water.

This minor correction has been neglected and source photons are allowed to cross the sphere containing the trace element more than once without any corrections.

If we want to give values of P per emitted source photon instead of per generated (= on the phantom incident) photon, we have to multiply with $\Omega_S/4\pi$ as discussed in section 2.2. If this is done, the parameter is denoted by P_S . The parameter P (or P_S) is only directly proportional to the number of detected characteristic photons if we can make the approximation that the sphere V is a point source emitting the characteristic X-rays. This approximation has been considered justifiable in the calculations performed in this work.

Since we have made this approximation, we may study the influence from various detector geometries on P by applying the weighting factor $\Omega_D/4\pi$, where Ω_D is the solid angle of detector as seen from the centre of the sphere. Assuming that the detector collimator is large enough not to interfere. If this is done, the parameter is denoted by P_D .

If the change in detector geometry also includes a change in the distance between the centre of the sphere V and the detector collimator, we have to correct for the attenuation of the K_α -photons.

$$P_{\text{corr.}} = P \cdot \left\{ \frac{\Omega_S}{4\pi} \cdot \frac{\Omega_D}{4\pi} \cdot e^{-\mu_W \cdot R_1} \right\} \quad 2.9.2$$

$P_{\text{corr.}}$ denotes here the corrected P value modified to allow for factors not directly included in the Monte Carlo calculations. However, only $P_{S,D}$ has been considered in this work.

Since rather extensive approximations are made in calculating values of this parameter, it must be used with care.

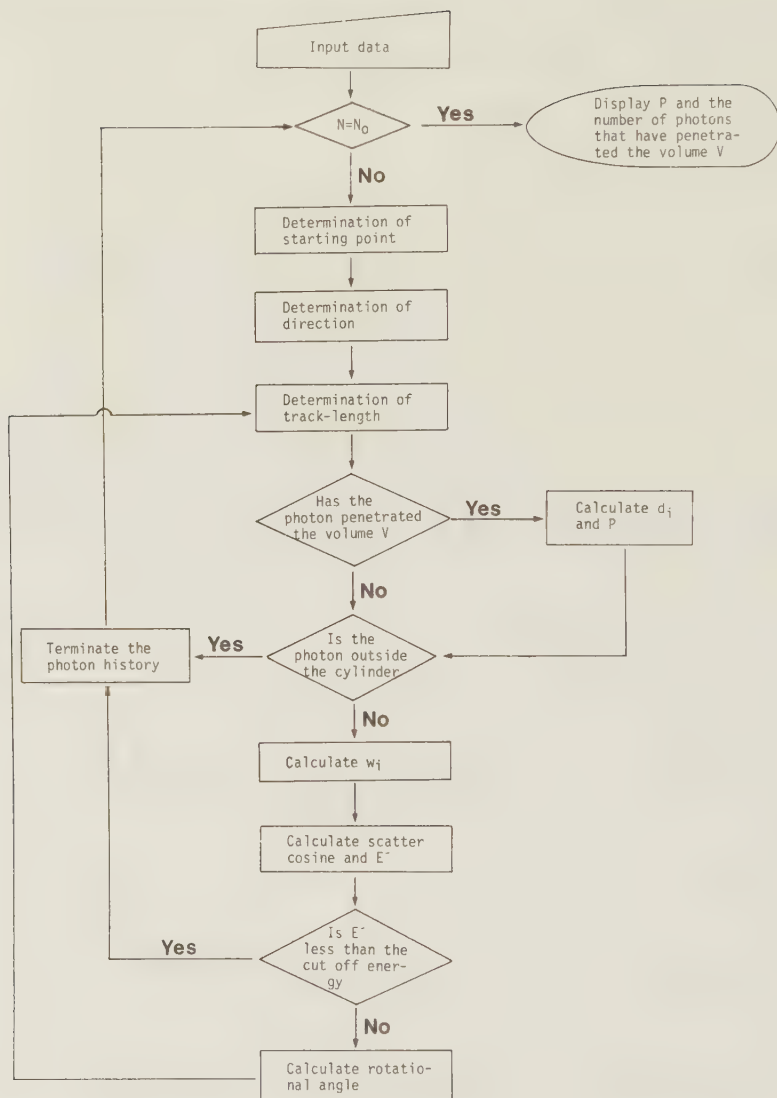
Calculation of scatter spectra

The scatter contribution is the factor limiting the detectability in all applications of X-ray fluorescence analysis and is especially troublesome when measuring in vivo, due to large scattering volumes. It must therefore be considered important to be able to study the magnitude of this interfering parameter. When a scattered source photon leaves the cylinder (described in section 2), the programme tests if 1) the photon has escaped through the detector collimator and 2) its direction is such that it can cross the detector. If the answer to these two questions is positive, the photon will be registered by the programme. If we assume that the photon lies in energy interval $h\nu \pm \frac{\Delta h\nu}{2}$, its weight w_n is added to the corresponding vector element $N_{h\nu}$, thereby contributing to the creation of a scatter spectrum. In the programme, it is also possible to differentiate between photons scattered 1, 2 and more than 2 times. If this possibility is used and the photon has been scattered n times, w_n is added to the matrix element $N_{h\nu,n}$.

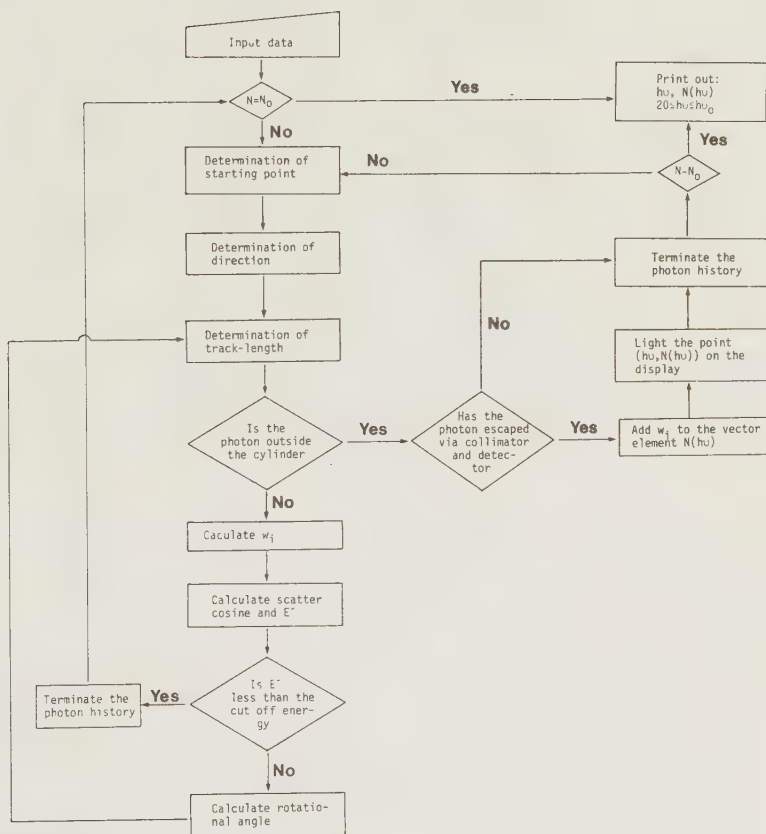
2.10 Flow diagrams of the Monte Carlo programme

The parameter P and the scatter spectrum are calculated separately and the flow diagrams used for the calculations are given below.

Flowdiagram for calculating P



Flowdiagram for calculations of scatter spectra



3 THE COMPUTER

The computer for which this Monte Carlo code has been developed is an ABC-80 microcomputer containing an eight-bit processor (Zilog Z-80) and a data memory consisting of 16 K RAM.

This computer can be incorporated into the XRF-system and is used in the administration of the in vivo XRF-measurements.

The computer is programmed in BASIC which makes it rather slow, but its ready availability somewhat compensates for this disadvantage.

A very important factor in Monte Carlo calculations is the generation of random numbers.

The random number generator in ABC-80 is written in Assembler and works with a word length of 35 bits. To generate 1 random number takes 11 ms. The period of this random generator is very long, about 10^9 numbers. The quality of the generator is investigated by means of the sample moments $\frac{1}{n} \sum \xi_i$ and $\frac{1}{n} \sum \xi_i^2$. A perfect sequence of random numbers would have the values 1/2 and 1/3 respectively. The relative frequencies N_I/N_0 in the intervals $\{0 - 0.1\}$, ----- $\{0.9 - 1.0\}$, have also been studied. The ideal values of these relative frequencies considering the uniform distribution would of course be 1/10. The results given in table 3 indicate that the random numbers may be uniformly distributed to an acceptable degree, which is of the utmost importance for making accurate Monte Carlo calculations.

Table 3 Test of the quality of the random number generator by studying 5 sequences each containing 1000 random numbers ξ_i

Seq.	$\bar{x}$	$\bar{x}^2$	Relative frequency									
			0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
1	0.500	0.334	0.091	0.111	0.108	0.098	0.096	0.100	0.107	0.088	0.086	0.115
2	0.486	0.322	0.118	0.087	0.110	0.109	0.103	0.097	0.084	0.100	0.094	0.098
3	0.500	0.334	0.099	0.107	0.103	0.084	0.105	0.095	0.093	0.115	0.105	0.094
4	0.509	0.343	0.096	0.094	0.098	0.111	0.093	0.094	0.105	0.096	0.096	0.117
5	0.498	0.332	0.107	0.101	0.099	0.088	0.109	0.093	0.108	0.093	0.101	0.101
Mean	0.499	0.333	0.102	0.100	0.104	0.098	0.101	0.096	0.099	0.098	0.096	0.105

4 THE Ge-DETECTOR

The detector used is a 1 cm^3 ($16 \text{ mm } (\phi) \times 5 \text{ mm}$) high-purity Ge-detector (Princeton Gamma Tech, Frankfurt, West-Germany). The detector is connected via a pulsed optical feedback preamplifier and a pulse-shaping linear amplifier to an 80 MHz analog-to-digital converter. A base-line restorer was used to maintain the energy resolution at the high countrates used (around 10^4 s^{-1}).

When a photon of energy $h\nu_0$ penetrates the active volume of the detector, it may be registered by the detector system in a number of different ways depending on the interaction events that may occur. A brief summary of the processes involved in detecting photons is given below.

- a) The photon may be transmitted through the active volume without any interaction. The probability for such an occurrence is very small for energies below 80 keV.
- b) The energy $h\nu_0$ of the photon may be absorbed completely, which is the most probable occurrence for energies below approximately 120 keV.
- c) The photon may escape after a single compton scattering thereby giving rise to a pulse somewhere in the energy interval $]0, e_c]$, where e_c is the compton edge given by

$$e_c = h\nu_0 - \frac{h\nu_0}{1 + \frac{2h\nu_0}{m_0c^2}} \quad 4.1$$

- d) The photon may escape after multiple compton scatterings giving rise to a pulse somewhere in the energy interval $]0, h\nu_0[$.
- e) The primary photon of energy $h\nu_0$ or a photon previously scattered in the detector may be absorbed by photoelectric absorption. If this process is followed by the escape of a characteristic X-ray photon from Ge, a pulse corresponding to the energy $h\nu_0 - h\nu_{\alpha,(\beta)}$, will be registered, where $h\nu_{\alpha,(\beta)}$ denotes the energies of the characteristic K_α or K_β photons of Ge.
- f) Other factors influencing the observations are inherent detector properties such as linearity and incomplete charge collection, defected pulses (15) and also interactions with the surrounding material.

To convert the calculated energy distribution to a pulse-height distribution, the factors discussed above are quantitatively investigated by

means of the "full-energy peak efficiency" and the "response function".

The full-energy peak efficiency is defined as

$$\epsilon = \frac{\text{number of pulses in the full-energy peak}}{\text{number of photons incident on the detector}}$$

The diameter of the incident photon beam was 15 mm, and the diameter of the active area of the detector 16 mm according to the manufacturer. The experimental determination of ϵ as a function of photon energy was carried out by means of gamma ray sources of well-known activity. (Laboratoire de Métrologie des Rayonnements Ionisants, Gif-sur-Yvette, France).

The radionuclide sources used were ^{57}Co (14.4 keV, 9.76%: 122.06 keV, 85.6%: 136.5 keV, 11.04%), ^{109}Cd (88.035 keV, 3.79%), ^{139}Ce (165.8 keV, 79.9%) and ^{241}Am (26.3 keV, 2.4%: 59.54 keV, 35.7%).

The decay data for these radionuclides were taken from Lederer et al (14). The result of the investigation of the full-energy peak efficiency is shown in figure 10. For energies below 40 keV the efficiency for our detector is low compared to published data (16,17).

The number of pulses N'_C per energy interval ($\Delta h\nu = 1$ keV) below the Compton edge e_c , which are due to escape after single Compton scattering, has been derived from Monte Carlo calculations. These calculations were carried out for a Ge(Li)-detector of the same size as ours and are discussed by Svahn (16).

The variation of N'_C/N_0 (where N_0 denotes number of photons incident on the detector) with energy $h\nu_0$ is also given (16).

The number of registrations due to the escape of Ge - K_α and Ge - K_β photons are also derived (16) and have been calculated using the following analytical expressions:

$$\frac{N_\alpha}{N_0} = \frac{h\nu_0 \cdot K}{\overline{h\nu}_{\alpha\beta}} \cdot \frac{h\nu_\beta - \overline{h\nu}_{\alpha\beta}}{h\nu_\beta - h\nu_\alpha} \quad 4.2$$

$$\frac{N_\beta}{N_0} = \frac{h\nu_0 \cdot K}{\overline{h\nu}_{\alpha\beta}} \cdot \frac{\overline{h\nu}_{\alpha\beta} - h\nu_\alpha}{h\nu_\beta - h\nu_\alpha}$$

Here, K denotes that fraction of the primary photon energy which escapes the detector in the form of K_α - and K_β radiations. The value of K is

Full energy peak eff., ϵ

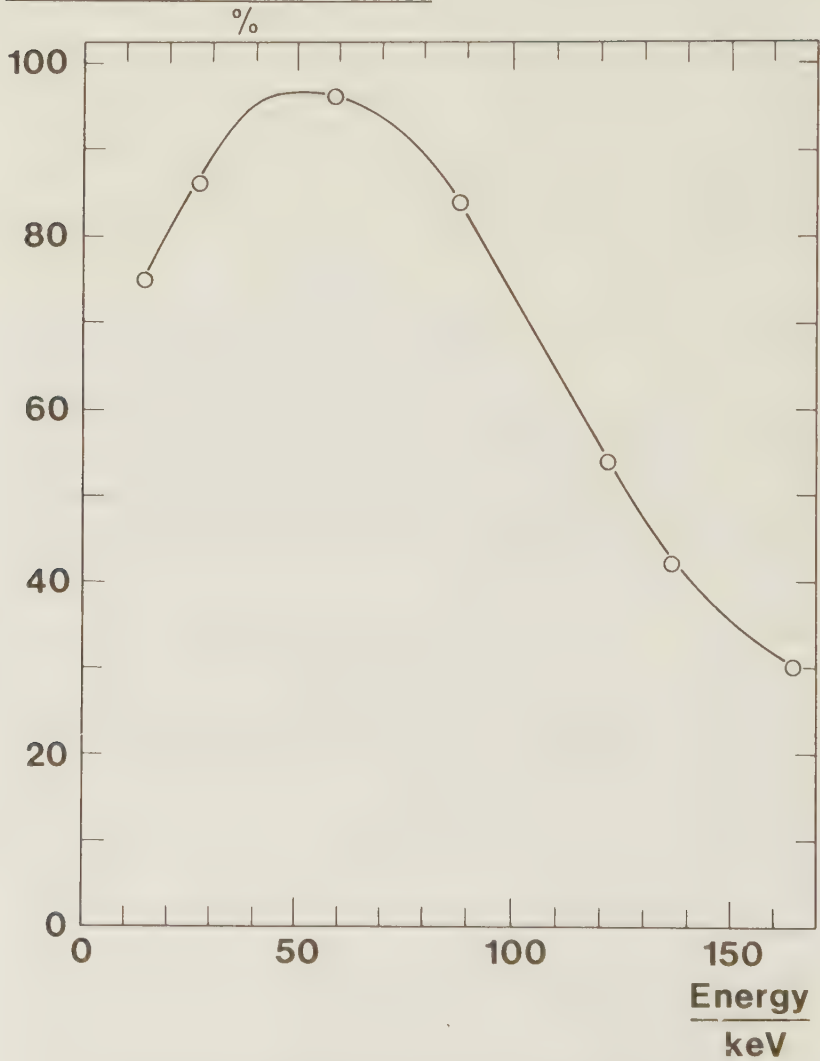


Fig. 10 Result of the experimental determination of the full-energy peak efficiency of the Ge-detector.

determined by means of Monte Carlo calculations and its variation with energy $h\nu_0$ is given by Svahn (16).

In this work, however, we have made an experimental estimation of the number of pulses N_C'' per energy interval ($\Delta h\nu = 1$ keV), which are due to incomplete charge collection and other effects such as escape of photons after multiple scattering in the detector. The investigation was made with a ^{241}Am source with a 0.8 mm Pb-filter so as to reduce the number of low-energy photons reaching the detector. A comparison of the pulse-height distribution from ^{241}Am with and without the Pb-filter shows that the influence from photons scattered in the Pb-filter is negligible. We also used 140 keV photons from a $^{99}\text{Tc}^m$ solution placed on a filter paper surrounded by thin plastic film. The mean number of counts, N_C'' , per energy interval per incident photon N_0 varies between 0.0029 for photons of energy 59.5 keV and 0.0016 for photons of energy 140 keV. In terms of the numbers of photons registered in the full-energies peaks, these values are 0.003 and 0.004 respectively.

This contribution to the response is assumed to be due to 1) incomplete charge collection, 2) photons interacting in the material surrounding the active detector volume before entering it and 3) to some extent, to the escape of photons multiply-scattered in the active detector volume. The effects discussed above may give a contribution over the entire energy range from zero to the near vicinity of the incident photon energy. According to the discussion and the results presented here, a photon of energy $h\nu_0$ incident on the detector is assumed to give rise to a pulse-height distribution of the form:

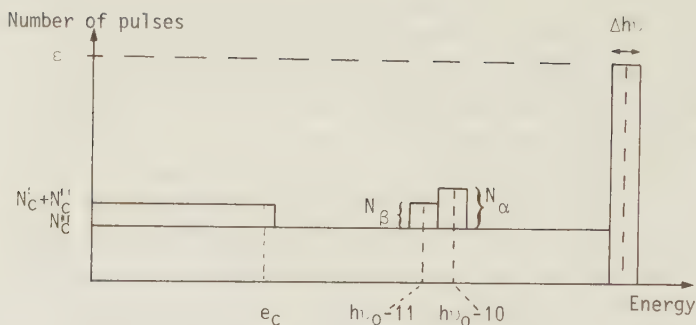


Fig 11 The pulse-height distribution given by the Ge-detector from an incident photon of energy $h\nu_0$ (schematically drawn, not to scale)

In the energy range $]0, e_c + \frac{\Delta h\nu}{2}]$ the pulse-height distribution is assumed to be the sum of pulses N'_C due to escape after single Compton scattering in the detector and pulses N''_C due to incomplete charge collection and escape of photons after multiple scattering in the detector etc.

5 VALIDITY OF THE SIMULATED GEOMETRY

To check whether the cylindrical phantom is a valid approximation to a typical in vivo X-ray fluorescence situation, we have compared experimental pulse-height distributions obtained by using a cylindrical water phantom of diameter 60 mm, identical to the simulated phantom, to pulse-height distributions obtained by a full-size phantom. The radiation sources used in this investigation were ^{241}Am (59.54 keV) and ^{57}Co (122, 136 keV) in the following geometry:

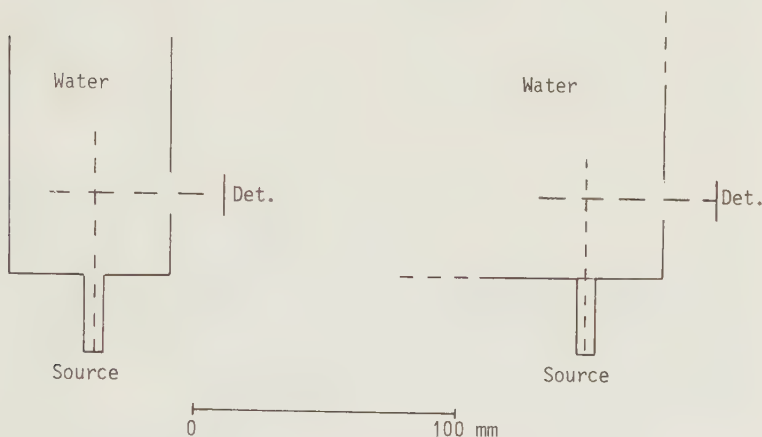


Fig 12 Experimental set-up used for investigating the validity of the cylindrical phantom used in simulating in vivo X-ray fluorescence analysis

The result of this investigation was that there are no differences in the pulse-height distributions obtained from the cylindrical phantom and from the full-size phantom. Some minor relative increase in the low-energy part of the scatter spectrum would have been expected using the "body size"-phantom due to the increased number of multiply-scattered photons reaching the detector. This was, however, not observed, even for energies as high as 122 and 136 keV (^{57}Co).

6 CALCULATION OF SCATTER SPECTRA AND CONVERSION TO PULSE-HEIGHT DISTRIBUTIONS

The influence on the calculated scatter spectra of the method used to sample the Klein-Nishina function has been investigated using 60 keV primary photons and the following geometrical parameters

Source diameter	4 mm
Source-coll. diameter	: 4 mm
l_1	: 30 mm
l_2	: 30 mm
Diameter of cylinder	: 60 mm
Width of detector coll.	: 16 mm
Width of detector	: 16 mm
Distance from origin to the detector	: 50 mm

In figure 13 are shown the two scatter spectra obtained by the rejection technique and the inverse function method. It is clearly seen in this figure that the underestimation of scatter angles greater than 90° in the inverse function method (see fig 8,9) has a significant influence on the low energy part of the spectrum. This means that we have one fairly fast method which is not totally accurate and one somewhat slower method in which the Klein-Nishina function is sampled correctly.

To make it possible to choose the method used from case to case, both are included as subroutines in the programme. The rejection technique has, however, been used in all calculations presented in this work.

A general investigation of the structure of the scatter spectra taking into account the number of compton scatterings of the registered photons in the phantom, has been performed for 60 keV photons (^{241}Am) and 122 and 136 keV photons (^{57}Co). The geometrical parameters given above were used in these calculations. In figure 14 is shown the calculated scatter spectrum obtained from primary photons of energy 60 keV. It is obvious that the number of scattered photons with energies below 30 keV reaching the detector is very small. It is also clear that photons singly-scattered at about 90° dominate over the multiply-scattered photons reaching the detector. The scatter spectrum above, converted to a pulse height distribution according to section 4, is shown in figure 15. The figure also includes the corresponding experimentally determined pulse-height distribution and good agreement is obtained. When comparing figures 14 and 15

it is obvious that the interfering background distribution obtained in measurements of iodine ($I K_{\alpha}$: 28.5 keV) is to a very high degree caused by the detector. This is supported by the results given in ref 18, where a Ge- and a Si(Li)-detector are compared in identical in vivo situations. Figure 16 shows the scatter spectrum obtained with 122 and 136 keV photons with relative frequencies of 87.2% and 12.8% respectively corresponding to the decay data of ^{57}Co .

For platinum ($\text{Pt } K_{\alpha}$: 66.2 keV), the scatter contribution is more prominent than when detecting iodine using 60 keV photons.

The relation between singly-scattered and multiply-scattered photons reaching the detector is approximately the same as for 60 keV photons, but the width of the energy-distribution is much greater, of course, in accordance with expectations.

The ^{57}Co source used in our experiments has a backing of wolfram. This means that wolfram K_{α} - (59 keV) and K_{β} -photons (67 keV) penetrate the water phantom and so contribute to the scatter spectrum.

The scatter spectrum of figure 16 converted to a pulse-height distribution is shown in figure 17 together with the converted scatter spectra of wolfram K_{α} - and K_{β} -photons.

Agreement between the calculated and measured pulse-height distributions (also given in figure 17) is good considering the complexity of the scatter spectrum. When comparing figure 17 and 18 it is clear that in so far as the detection of platinum is concerned, the detector response has an influence on the background contribution, however, not as much as in the case of iodine detection.

Registrations per energy interval

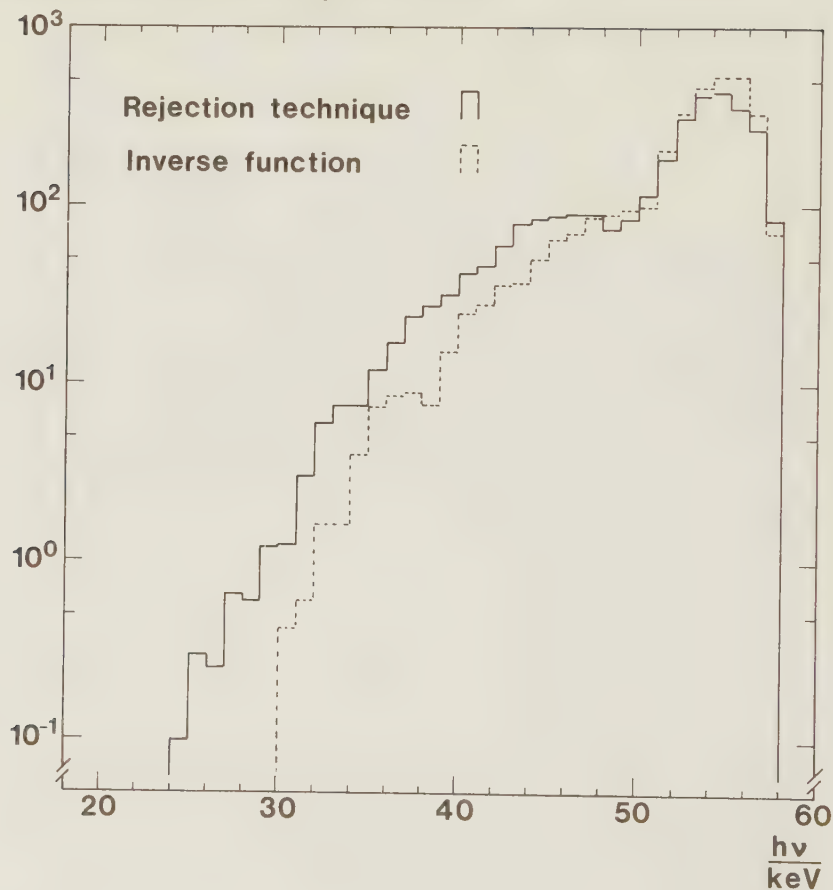


Fig. 13 Energy distribution of scattered photons obtained by two different methods of sampling the Klein-Nishina function.

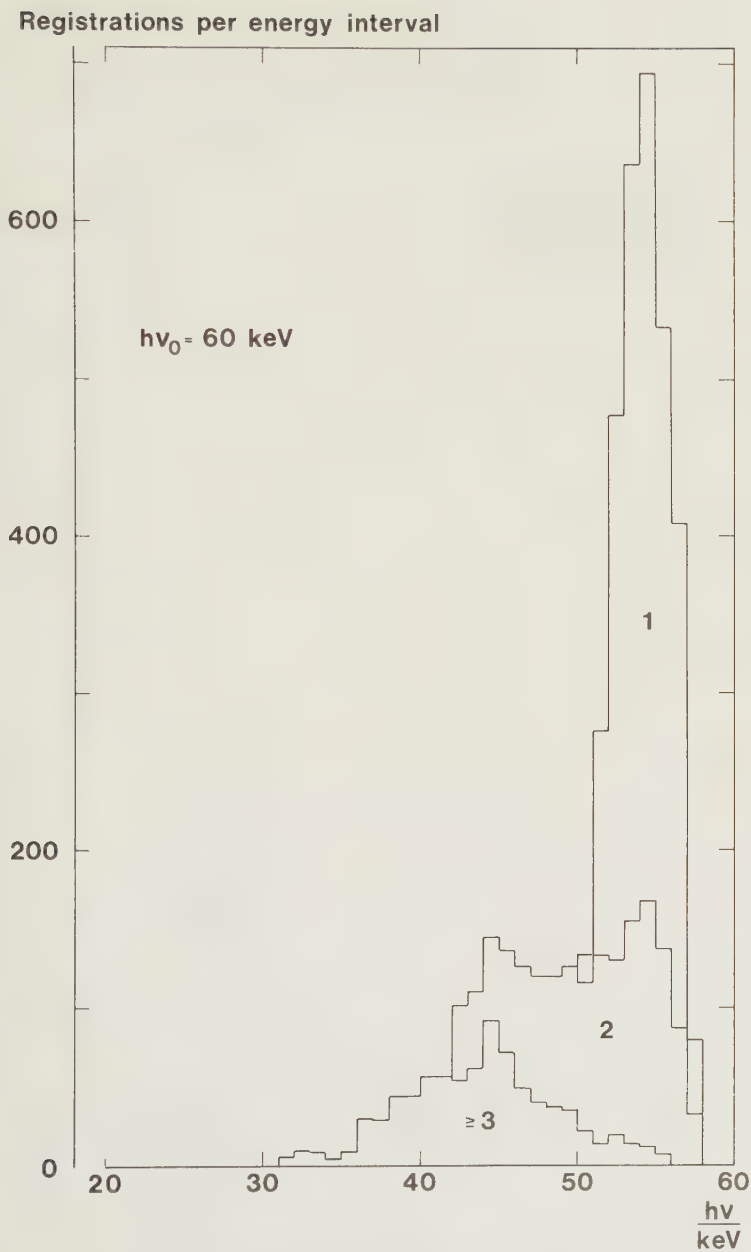


Fig. 14 Calculated energy distribution of photons, which have been scattered in the phantom 1, 2 and more than 2 times respectively.

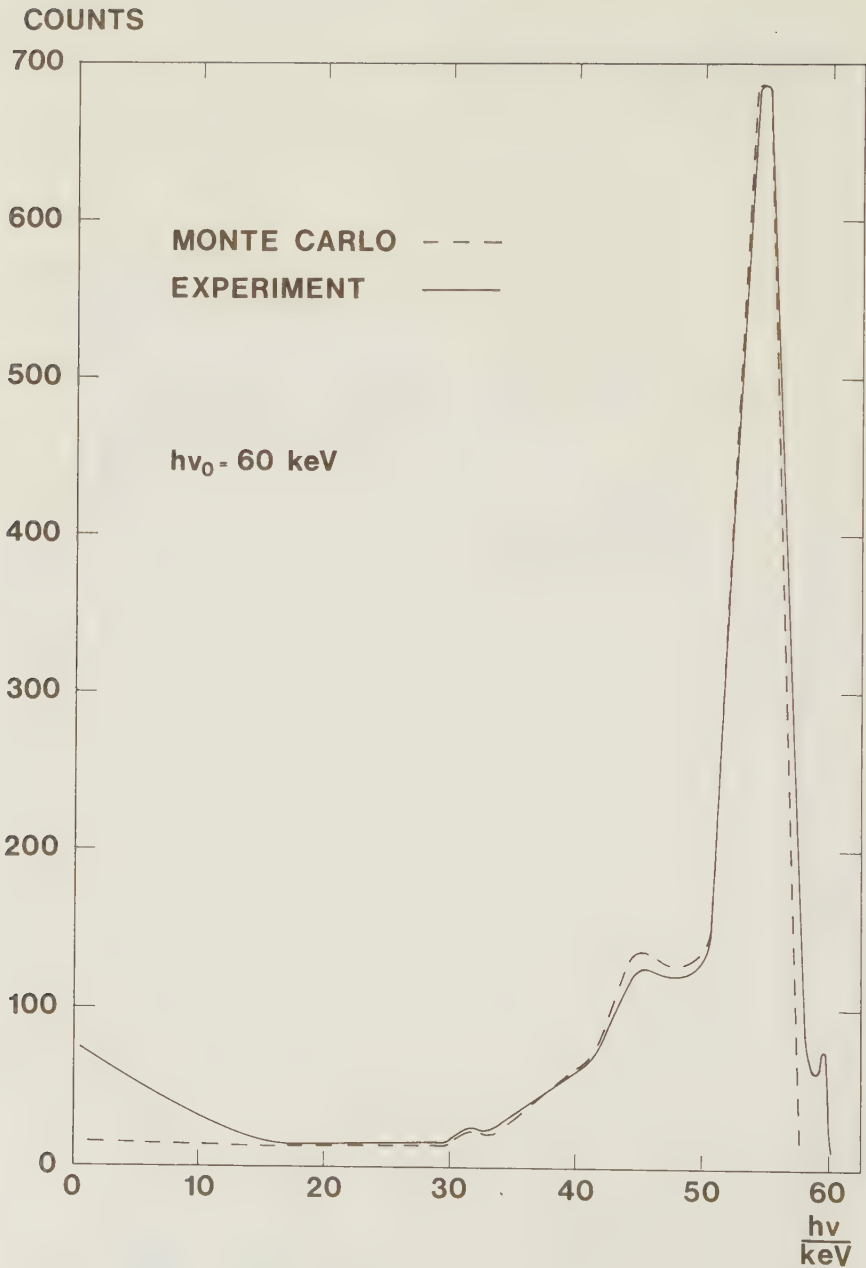


Fig. 15 Calculated and experimentally obtained pulse height distributions from the Ge-detector (5mm x ϕ 16mm).

Registrations per energy interval

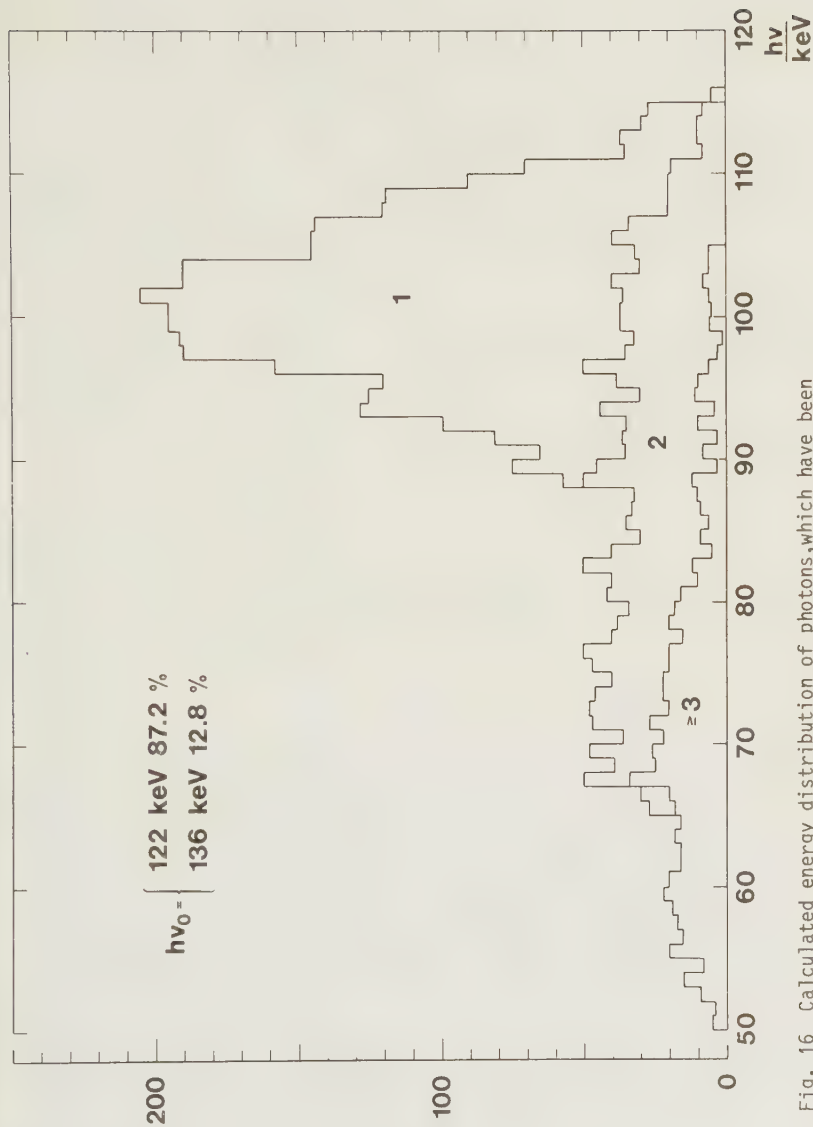


Fig. 16 Calculated energy distribution of photons, which have been scattered in the phantom 1, 2 and more than 2 times respectively.

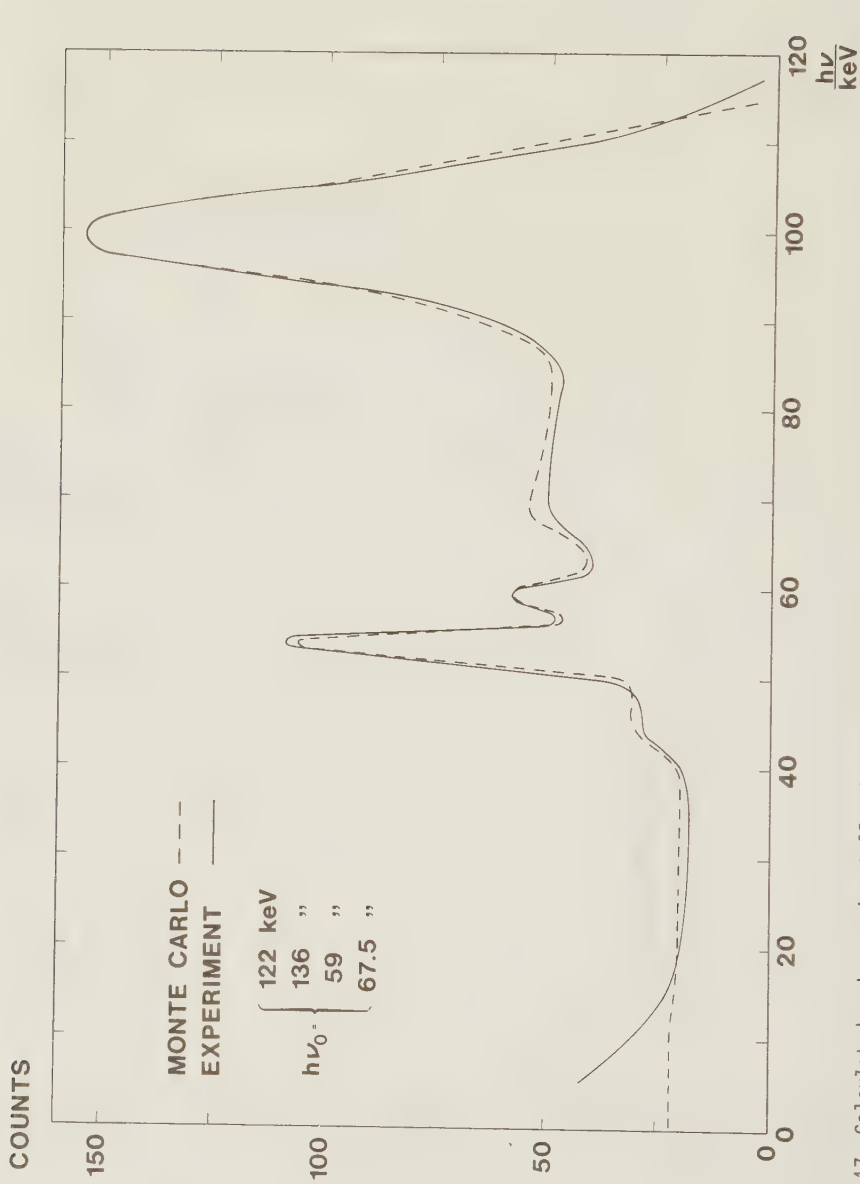


Fig. 17 Calculated and experimentally obtained pulse height distributions from the Ge-detector (5mm x ϕ 16mm). The primary energies 59 keV and 67.5 keV are due to the wolfram backing in the Co-57 source.

7 CALCULATION OF $P_{S,D}$, THE SCATTER CONTRIBUTION AND MINIMUM DETECTABLE CONCENTRATION

The parameter P

The value of $P_{S,D}$ has been studied for a sphere containing iodine or platinum. The primary photon energies studied were 60 keV (^{241}Am) for iodine and 122 and 136 keV (^{57}Co) for platinum.

The influence of different diameters of the source collimator (constant detector geometry) and different detector geometries (constant source geometry) on the $P_{S,D}$ value has been studied.

The geometry used for this investigation is that given in figure 2, geometrical parameters being as follows:

(1) Variation with source geometry

Source diameter	: 4 mm
Source-coll. diameter	: 4-24 mm
l_1	: 30 mm
l_2	: 30 mm
Diameter of cylinder	: 60 mm
Diameter of sphere	: 10 mm
Detector-coll. width	: 16 mm
Detector	: 16 mm
Distance from the origon to the detector	: 50 mm

(2) Variation with detector geometry

4 mm
4 mm
30 mm
30 mm
60 mm
10 mm
10-36 mm
10-16 mm
50 mm

In figure 18 is given the variation in the $P_{S,D}$ value with varying source collimator. This figure gives that when considering the amount of generated characteristic photons it is advantageous to have a source collimator size which gives a beam diameter at depth l_1 moderately exceeding the diameter of the sphere. The reason for this is of course that more photons per unit time are penetrating the phantom (or body). Photons passing the sphere before their first interaction may be scattered in a direction which permits them to cross or penetrate it and thereby contribute to $P_{S,D}$.

When varying the detector geometry the $P_{S,D}$ value is only influenced by the solid angle of the detector as seen from the centre of the sphere (Ω_D). The $P_{S,D}$ values multiplied by $\Omega_D/4\pi$ corresponding to the different detector geometries are given in table 4.

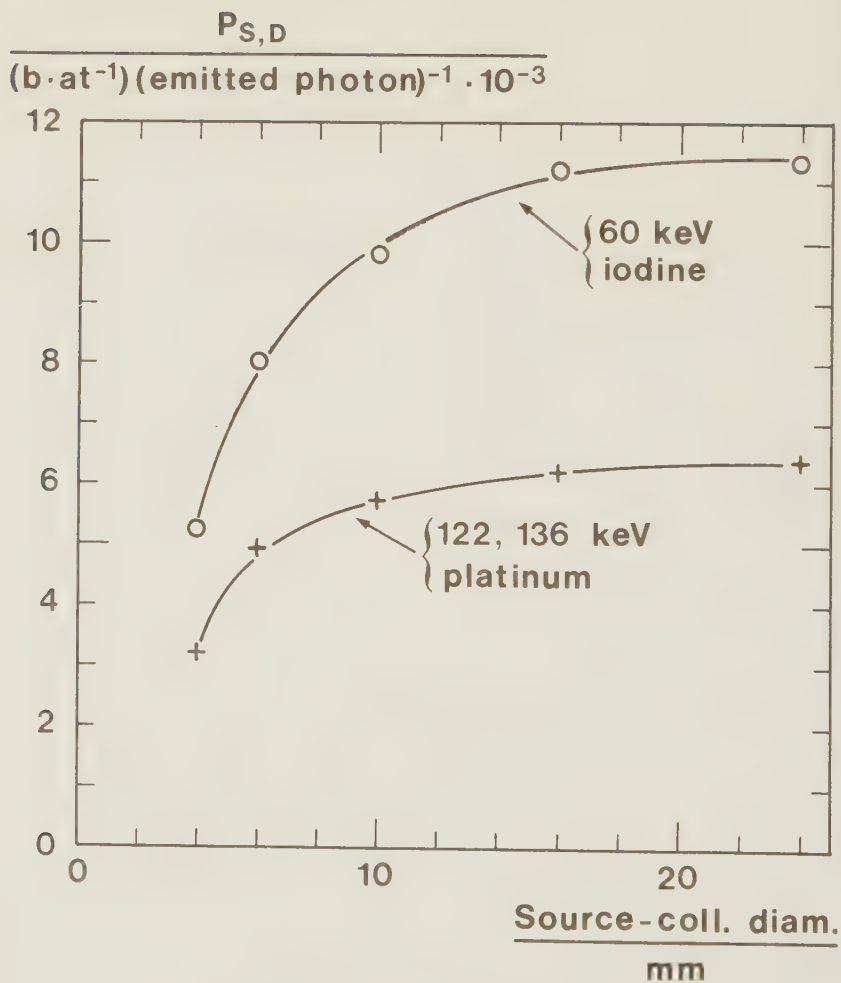


Fig. 18 The variation in $P_{S,D}$ by diameter of the collimator in front of the source, for detection of iodine by simulating an Am-241 source for excitation and of platinum by simulating a Co-57 source

Table 4 The influence of variations in detector geometry on the value of $P_{S,D}$, the scatter-contribution b and $(\sqrt{b}/P_{S,D})^{\sim}$ MDC
 $P_{S,D}$ and b are normalized to 10^5 emitted source photons $\{(\Omega_S/4\pi) = 0.0011\}$.

Primary photon energy, 60 keV; trace element I					
C {mm}	D {mm}	$\Omega_D/4\pi$	$P_{S,D}$	b	$\sqrt{b} / P_{S,D}$
10	10	0.0025	165	0.008	$0.54 \cdot 10^{-3}$
13	13	0.0042	277	0.012	$0.40 \cdot 10^{-3}$
16	16	0.0063	416	0.018	$0.32 \cdot 10^{-3}$
24	16	- " -	- " -	0.023	$0.36 \cdot 10^{-3}$
36	16	- " -	- " -	0.027	$0.39 \cdot 10^{-3}$

Primary photon energies 122, 136 keV; trace element Pt					
C {mm}	D {mm}	$\Omega_D/4\pi$	$P_{S,D}$	b	$\sqrt{b} / P_{S,D}$
10	10	0.0025	129	0.019	$1.07 \cdot 10^{-3}$
13	13	0.0042	216	0.039	$0.91 \cdot 10^{-3}$
16	16	0.0063	323	0.052	$0.71 \cdot 10^{-3}$
24	16	- " -	- " -	0.068	$0.81 \cdot 10^{-3}$
36	16	- " -	- " -	0.079	$0.87 \cdot 10^{-3}$

The background contribution

The background contributions, denoted in the following text by (b), to the energy interval ($\Delta E=1$ keV) around the I K_{α} energy (28.5 keV) from 60 keV primary photons and in the energy interval ($\Delta E=1$ keV) around Pt K_{α} energy (65 keV) from 122 and 136 keV photons have been studied with different detector geometries (according to geometry (2) given above).

In table 4 the result of this investigation are given. As expected, the value of b not only depends on the size of the detector but also increases with the increasing size of the collimator.

Minimum detectable concentration

In order to study the possibility of making quantitative determinations of the amounts of trace element by means of X-ray fluorescence analysis, the minimum detectable concentrations MDC for a specific experimental situation is estimated by

$$\text{MDC} = \frac{3 \cdot C_0 \cdot \sqrt{b_e \cdot A}}{a_e \cdot A} \quad 7.1$$

(index e denotes experiment)

Here, a_e is the net countrate in the energy-interval containing the K_{α} -peak of interest and b_e is the background countrate in the same energy-interval. A denotes the analyzing time related to MDC and C_0 the concentration of the trace element. The factors in the formula is accounted for by the fact that the value of a_e should be at least three times the standard deviation of b_e for the trace element to be detectable.

Considering a constant analyzing time A, we can write

$$\text{MDC} \sim \frac{\sqrt{b_e}}{a_e} \quad 7.2$$

As discussed in section 2.9, the parameter $P_{S,D}$ is proportional to the number of characteristic photons detected. According to section 2.4, we know that it is possible to calculate a true pulse-height distribution from scattered primary photons. From this pulse-height distribution,

we may determine the scatter contribution (b) in the energy-interval of interest. We may now write

$$\begin{aligned} P_{S,D} &\sim a_e \\ b &\sim b_e \\ \text{MDC} &\sim \frac{\sqrt{b}}{P_{S,D}} \end{aligned} \quad 7.3$$

The expression in equation 7.3 has been used to study the influence of varying detector geometry (geometry (2)) on the minimum detectable concentration MDC.

The result of this investigation is shown in table 4.

It is obvious that the size of the detector is the most important parameter influencing the MDC value. One might a priori have expected that a very narrow collimation of the detector should be more advantageous due to reduction of the scatter contribution but this is not the case. Since the exact distribution of the trace-element is seldom known in in vivo measurements, one conclude that it is better to use a large collimator to make sure that the entire distribution is seen by the detector.

8 SUMMARY AND CONCLUSIONS

The Monte Carlo code constructed in this work has shown to be a valuable instrument in making theoretical studies of different in vivo X-ray fluorescence situations.

The results of investigations of the Ge-detector give that the full-energy peak-efficiency for photons below 40 keV is lower than has been reported by others (16,17). The response function of the Ge-detector evaluated in this work seems to be in agreement with the results given in refs 15,18. A thorough knowledge of the detector response function is needed to be able to convert the Monte Carlo calculated scatter spectra to pulse-height distributions. Comparison of a calculated scatter spectrum and a pulse-height distribution measured when detecting iodine in vivo using primary photons of energy 60 keV (^{241}Am) shows that the background contribution is produced in the detector itself (compare ref 18). One might have expected that the background contribution was mainly due to primary photons multiply-scattered in the phantom (or body).

The calculation of this scatter spectrum also shows that the photons singly-scattered at around 90° which reach the detector dominate over the multiply-scattered photons. One may then conclude that polarization of the primary photons could be a successful method in reducing the background and thereby lowering the limit of detection of iodine.

When photon energies of 122 and 136 keV are used for the detection of platinum, the situation is not the same. The results of the comparison between the scatter spectrum and the corresponding pulse-height distribution shows in this case that the background contribution consists to a higher degree of photons multiply-scattered in the phantom (or body).

A parameter denoted P has been defined in this work, which is (under certain conditions) proportional to the amount of generated and detected characteristic photons of some trace-element. This parameter has been shown to be valuable for the estimation of a relative measure of MDC. The investigation of the influence of the detector geometry on the minimum detectable concentration of trace-elements shows that it is advantageous to choose a large detector and a large detector collimator. This conclusion is important when the concentration of the trace-element is low and when the size and location of the distribution is not well known. This situation is common in in vivo applications of X-ray fluorescence analysis.

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MONTE CARLO DETERMINATIONS OF OPTIMAL PHOTON ENERGIES FOR XRF ANALYSIS OF IODINE IN VIVO

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INTRODUCTION

After the pioneering work of HOFFER et al.¹ on fluorescent scanning of natural iodine in the thyroid, several authors have suggested the use of X-ray fluorescence analysis to follow in vivo the distribution and elimination of stable tracers injected prior to the investigation. The normal method of performing such studies is to inject iodine containing contrast media and then follow the variation in iodine concentration by in vivo measurements over the organ or tissue of interest^{2,3}.

A theoretical treatment of the application of X-ray fluorescence in in vivo studies has been made by TINNEY⁴ by means of analytical calculations.

Sources of ^{241}Am , emitting mainly 59.5 keV photons, are often used for the excitation of K_{α} - X-rays from iodine. The aim of the present work is to study if this photon energy is optimal for the analysis of iodine in various in vivo situations. For this purpose, we have used Monte Carlo calculations to determine the amount of K_{α} -photons generated per primary photon as well as the contribution from interfering scattered primary photons, which together give an estimate of the minimum detectable concentration. The results of the calculations of scatter spectra are compared with experimental data at a primary photon energy of 59.5 keV (^{241}Am).

METHOD

Monte Carlo simulation: The system to be modelled is a disc-shaped well collimated radionuclide source, a water phantom with an iodine-containing volume inside and a collimated detector (Fig. 1).



Fig. 1. Simulated experimental set up

To reduce the number of photons rejected in the calculations, the collimator and detector were allowed to rotate around the water phantom (around the y-axis). The MC calculations were carried out on a micro-computer with an eight-bit processor and a data memory consisting of 16 k RAM. The MC program is described briefly below:

- a. Photons are emitted from the source (S) parallel to the y-axis.
- b. Each pathlength of a photon in the water phantom is sampled according to $s = (1/\mu_T(E)) \cdot \ln \xi$ where $\mu_T(E)$ is the attenuation coefficient in water and ξ is a uniformly distributed random number⁵.
- c. In the energy interval of interest (20-60 keV), photons interact by photoelectric absorption and scattering. Only Compton scattering is taken into account in our calculations. Photon histories are not terminated subsequent to photoelectric absorption. Instead, photons gain a weighting factor $W_n = W_{n-1} \cdot (\mu_c(E_{n-1})/\mu_T(E_{n-1}))$, n denotes the number of interactions.

This is a well known method of variance reduction⁶.

- d. The Compton scattering angle θ is sampled according to the rejection method given by KAHN⁷. The angle θ and the rotational angle $\phi = \pi(2\xi - 1)$ give the direction towards next point of interaction.
- e. When a photon crosses the iodine-containing volume V, the program records the pathlength d in V, the photon absorption coefficient of I ($\tau^I(E)$) at energy E of that photon and the weighting factor W . There might be more than one cross per photon history.
- f. If the scattered photon (r) escapes from the phantom through the collimator opening (C) and the detector (D), its energy E and weighting factor W are registered, creating a scatter spectrum. Photon histories are terminated if the photons escape the phantom anywhere except through the collimator opening and the detector or if the energy E falls below 20 keV.

The cross section data used in the program is taken from HUBBELL⁸.

Generation of $K\alpha$ -photons from I: Since iodine in the *in vivo* applications appears in trace element concentrations, it would be very impractical to calculate the absolute number of $K\alpha$ -photons generated by the MC-program. Instead, we have derived a quantity P which is proportional to this number:

$$P = \{ \sum_i \tau_i(h\nu) (d_i/d_{\max}) W_i \} / N_0 \quad \text{Eq 1}$$

Here N_0 is the number of primary photons generated in the source. The energy E in equation 1 lies between E_0 and the K-edge of I.

Calculated scatter spectrum and experimental comparison:

The calculated scatter spectra are converted to detector signal and compared with measured distributions. The measurements were made by a Ge-detector and a well collimated Am-241 source.

The energy interval around 28.5 keV is that of greatest importance since this is the region containing the $K\alpha$ -photons. The contribution from scattered primary photons in this region is called b .

Detection limit of I: The minimum detectable concentration (MDC) is proportional to $\sqrt{b/a}$ where a is the net countrate in the $K\alpha$ -peak and b the background countrate in this energy interval.

The quantity P discussed above is proportional to a , which means that a study of $\sqrt{b}/P$ yields the relative variation in MDC.

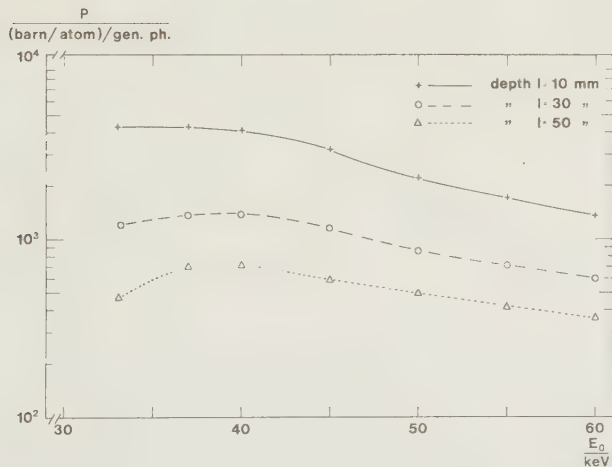


Fig. 2. The variation in P with primary photon energy E_0 and depth

RESULTS AND DISCUSSION

Generation of K α -photons from I: The relative variation in P is given in figure 2. It is obvious that the increase in τ^I with lower primary photon energies compensates for the loss of primary photons due to increasing attenuation in the phantom. Close to the K-edge the attenuation is too high to be compensated for by the increased τ^I which results in a lower value of P for greater depth. The very pronounced depth dependence in P is clearly seen in figure 2. The statistical uncertainty in P is less than 2 %.

Calculated scatter spectra and experimental comparison: Figure 3 compares a calculated scatter spectrum (converted to detector signal) and a measured distribution for a depth of 30 mm. As already mentioned coherent scattering is not included in the calculations. The calculated contribution b in the energy interval 28-29 keV is given in figure 4. As expected b increases with decreasing primary photon energy. The relative value of b is experimentally verified at $E_0=59.5$ keV. The statistical uncertainty in b is about 10 %.

Detection limit of I: The relative variation in $(\sqrt{b}/P) \cdot \text{MDC}$ is given in figure 5. The optimal photon energy for in vivo detection of I in geometries similar to the one used in this work is about 45 keV. However, the difference in $\sqrt{b}/P$ between 45 and 60 keV is only about 40 %. The statistical uncertainty in $\sqrt{b}/P$ is about 4 %.

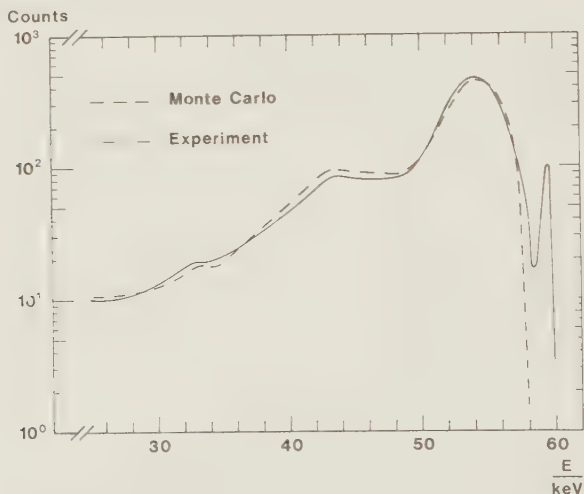


Fig. 3 Comparison of calculated and measured scatter distribution at a primary energy of 60 keV.

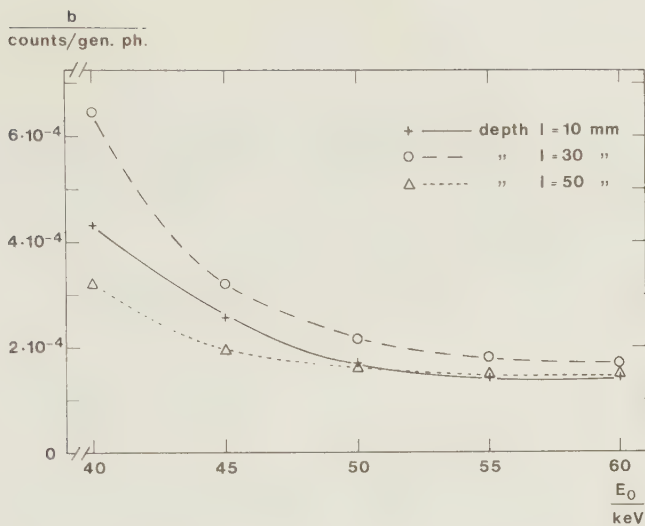


Fig. 4 Scatter contribution in the energy interval 28-29 keV

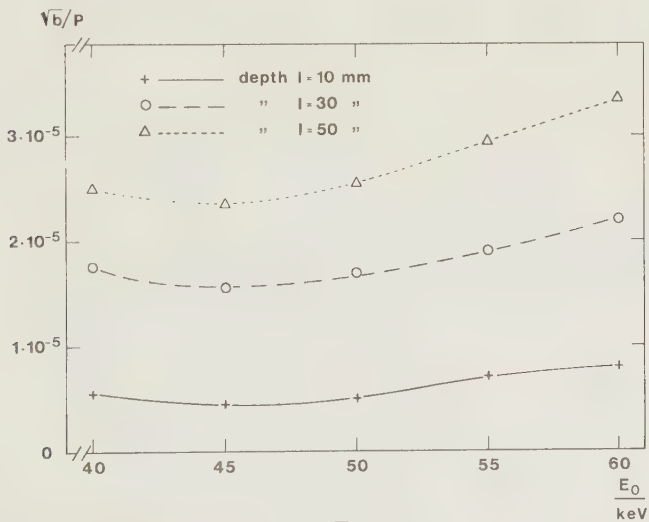


Fig. 5 The relative variation in $(\sqrt{b}/P) \sim \text{MDC}$ by primary energy E_0 and different depth l .

CONCLUSION

The MC calculations show that for organ depth down to at least 50 mm the number of K α -photons from I per primary photon has a maximum for primary energies very close to the K-edge of I. If, however, one considers the inevitable scatter contribution the primary energy which gives the best conditions of measurement is about 45 keV. If the primary energy is increased to 60 keV (Am-241), the detection limit is impaired by 40 %.

Considering the simplicity and mobility of Am-241 sources, it is doubtful whether the improvement of about 40 % theoretically possible by changing to the use of an X-ray tube with secondary target is justifiable.

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NON-INVASIVE ESTIMATION OF KIDNEY FUNCTION BY X-RAY
FLUORESCENCE ANALYSIS

Method for in vivo measurements of iodine-containing contrast
media in rabbits

(short title for running heads: Non-invasive estimation of
kidney function by XRF)

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ABSTRACT

An X-ray fluorescence technique has been used for quantitative non-invasive measurements of the concentration of iodine-containing contrast media in rabbits without the use of blood or urine sampling.

An 11 GBq ^{241}Am source ($E_{\gamma} = 59.5 \text{ keV}$) was used to generate the characteristic X-rays of iodine and a $1 \text{ cm}^3 \text{ Ge(Li)}$ -detector for registration of the I K_{α} radiation ($\bar{E} = 28.5 \text{ keV}$).

The nose of the rabbit offered the best measurement conditions and the minimum detectable concentration was $10 \mu\text{g}$ iodine per g tissue for a measuring time of 60 s.

The possibility of correcting for geometrical changes during the experiment using photons incoherently scattered at 90° has been investigated and found to be valuable in improving the precision.

The biological half-life of the contrast medium in the soft tissue part of the nose (measured in vivo) was similar to that in serum (measured in vitro), when determined in the period 2 - 4 hours after injection. In man, it was possible to follow the elimination of the contrast medium, by measurements on the finger tips, for at least 6 hours after an ordinary urography, and good correlation was observed between the biological half-lives of iodine in the finger tips and the serum samples.

The results indicate the possibility of being able to use the method for clinical evaluation of kidney function.

INTRODUCTION

The first clinical use of X-ray fluorescence analysis in vivo was to image the distribution of naturally-occurring stable iodine in the thyroid gland (HOFFER et al., 1968). Since then, reviews of the medical use of X-ray fluorescence analysis including measurements of iodine-containing contrast agents in vivo have been presented (HOFFER et al., 1971, KAUFMAN et al., 1973, KAUFMAN et al., 1978). Recently, the technique has also been shown to be valuable for the in vivo detection of lead (AHLGREN et al., 1976, BLOCH et al., 1976, SHAPIRO et al., 1978, AHLGREN and MATTSSON, 1979) and cadmium (AHLGREN and MATTSSON, 1980).

The iodine-containing contrast media used in urography are after their intravascular injection removed from the body mainly by renal excretion. During a period of several hours after injection, the rate of elimination of these media from the blood is directly related to renal function (compare Alazraki et al., 1975): the faster the kidneys excrete the medium, the faster it is removed from the blood.

It is the aim of the present work to investigate if an in vivo X-ray fluorescence technique can be used as a non-invasive method to determine the concentration and elimination rate of urographic contrast medium from living tissue and compare that rate with its elimination rate from serum.

MATERIAL

One rabbit was used to determine the region of the body offering the best conditions for measuring iodine in vivo. Seventeen living

rabbits were then used for estimating the elimination rate of contrast medium from their noses and from their blood. In nine of these rabbits the iodine concentration in their noses were measured also after sacrifice.

MEASUREMENT TECHNIQUE

An 11 GBq disc-shaped ^{241}Am -source of diameter 12 mm, emitting mainly 59.5 keV γ -rays, was used for generating the characteristic X-rays of iodine ($\bar{E}_{K_{\alpha}} = 28.5$ keV). To reduce the fluence rate of low energy photons emitted from the source, a 0.06 mm thick lead filter was placed in front of it. The collimator and the radiation shield were made of pure lead. A Ge(Li)-detector 16 mm in diameter and 5.2 mm thick with a Be entrance window 0.13 mm thick was used. Its energy-resolution (FWHM) was 450 eV at 28.5 keV. The mean angle between the incident and measured radiation was 90° for all measurements. The dead-time of the detector system during the in vivo measurements was about 25 percent of the total counting time.

To determine the iodine concentration in the rabbit nose in vivo the anaesthetized rabbit was reproducibly placed in supine position in a holder with its nose about 50 mm from the source and 50 mm from the detector (Fig 1).

The net count rate (a) of $\text{I } K_{\alpha}$ -X-rays and the count rate (n) of 59.5 keV photons incoherently scattered at around 90° (in the energy interval 52.3-54.8 keV) were measured. The count rate (a) is proportional to the number of iodine atoms in the irradiated volume seen by the detector and (n) to the total mass in that volume. To be able to correct for small changes in the amount of irradiated tissue, the method was calibrated in terms of the quotient $\frac{a}{n}$, denoted in the following text by R.

For calibration purposes, the soft tissue parts of the nose were excised immediately after sacrifice and about 2 g placed in a perspex test tube. Analysis of the samples gives the corresponding quotient $R'_{ts} = (\frac{a}{n})'_{ts}$, (where the prime denotes the test tube geometry and ts denotes tissue sample). The "normalized sensitivity", S'_{ts} , for iodine detection in the soft tissue in the test tube was determined by measurements in the test tube on a standard solution of well-known iodine concentration, C_s (where s denotes the standard solution). S'_{ts} is calculated according to equation 1

$$S'_{ts} = \frac{R'_s}{C_s} \quad \text{Eq (1)}$$

Using these symbols, eq 2 gives the iodine concentration, C_{ts} , in the tissue sample measured in a test tube.

$$C_{ts} = \frac{R'_{ts}}{R'_s} \cdot C_s = \frac{R'_{ts}}{S'_{ts}} \quad \text{Eq (2)}$$

The "normalized sensitivity" S_{nd} (where nd denotes the nose tissue of an intact dead rabbit) for detection of iodine in the soft tissue in that intact nose can now be determined from eq 3.

$$S_{nd} = \frac{R_{nd}}{C_{ts}} \quad \text{Eq (3)}$$

If the individual S_{nd} values show small variations from a mean value $\bar{S}_{nd}$, it is possible to estimate the iodine concentration C_{n1} (where $n1$ denotes nose tissue in living rabbit) in the nose of any rabbit using eq 4.

$$C_{n1} = R_{n1} / \bar{S}_{nd} \quad \text{Eq (4)}$$

In order to study possible effects on S_{nd} due to anatomical variations, rabbits of different weights (1.75-3.10 kg) (see table 1) were used for the calibrations. During measurements, the heads of the rabbits were to some extent fixed, but they could occasionally move their noses during the examination period. The influence of such movements in the size of the K_{α} -peak and the Compton distribution was determined by measurements on a dead rabbit.

To determine the elimination rate of the contrast agent from the rabbit, nose measurements were made about every ten minutes up to four hours after the injection and the iodine concentration was calculated using equation 3. The measuring times varied from 60 to 600 seconds depending on the iodine concentration, where 60 seconds were used for a concentration of about $1200 \mu\text{g}\cdot\text{g}^{-1}$ ($a \approx 13000 \pm 123$ counts) and 600 seconds for a concentration of $10 \mu\text{g/g}$ ($a \approx 1400 \pm 130$ counts).

Serum samples were collected at 30 minute intervals during the first 2 hours and at 20 minute intervals 2-4 hours after the injection. Urine was collected in periods of 30 minutes 15-105 minutes after the injection and after that in periods of 20 minutes. The serum and urine samples were measured in the test tubes.

RESULTS AND DISCUSSION

Measurements on different regions (thigh, ear, nose and paw) of a rabbit sacrificed one hour after injection of the iodine-containing contrast medium showed that the largest $I K_{\alpha}$ peak-to-background ratio was obtained when parts of the nose or the thigh were used as the measurement volume.

Table 1 lists the results of the in vitro measurements of C_{ts} for

the nine individual rabbits as well as the "normalized sensitivity", S_{nd} , for the different measurements of the intact noses. The "normalized sensitivity" S_{nd} is defined above as the ratio between R_{nd} and the tissue concentration C_{ts} (measured in vitro). For the nine rabbits, the median value and the range of its normalized sensitivity were found to be $3.16 \cdot 10^{-5} (\mu\text{g/g})^{-1}$ and $(3.42 - 3.01) \cdot 10^{-5} (\mu\text{g/g})^{-1}$, respectively. This gives a relative range of 13 percent.

The mean value of the individual "normalized sensitivity", $\bar{S}_{nd}$, was calculated to be $3.18 \cdot 10^{-5} (\mu\text{g/g})^{-1}$ and this value has been used to convert the individual R_{n1} values to iodine concentrations, C_{n1} . The minimum detectable concentration, MDC, was determined to about $10 \mu\text{g/g}$ for a measuring time of 60 seconds according to the relation
$$\text{MDC} = \frac{3 \cdot C \sqrt{b \cdot t}}{a \cdot t}$$
 where b is the background count rate and t the time in seconds.

There is no evidence for a systematic variation in S_{nd} with the weights of the rabbits. For the different nose positions possible, the maximum relative deviations in a and R are found to be 52% and 22% respectively, which indicates the validity of using R instead of a in calculating the iodine concentration.

The relation between the count rate of the $I K_{\alpha}$ -photons and the I -concentration in our in vitro measurements of serum and blood was found to be linear below $10\,000 \mu\text{g/g}$. Above this value, the relation between count rate and I -concentration is no longer linear due to increasing absorption of both the exciting radiation and the characteristic X-rays at iodine and hence a careful study was made to determine its form.

The iodine concentration interval for serum was about $10 - 2000 \mu\text{g/g}$. For the urine samples the interval was $1000 - 200\,000 \mu\text{g/g}$. The mini-

mum detectable concentration (MDC) for a counting time of 60 seconds was 4 $\mu\text{g/g}$.

Figure 2 shows the iodine retention curve for one rabbit as measured in vivo and the results of in vitro measurements of iodine concentration in serum.

Figure 3 shows the relation between the biological half-lives recorded in vivo (nose $T_{1/2}$) and in vitro (serum $T'_{1/2}$) during the period 2-4 hours after injection. Over the wide range of half-lives (35-160 min.), the relation between $T_{1/2}$ and $T'_{1/2}$ is given by $T'_{1/2} = (0.89 \pm 0.08) \times T_{1/2} + (4 \pm 5)$.

The correlation between $T_{1/2}$ and $T'_{1/2}$ is found to be good ($r = 0.94$).

Since $T'_{1/2}$ serum and $T_{1/2}$ nose (in vivo) in the present investigation are approximately the same, measurements of the $T_{1/2}$ nose (in vivo) gives information about $T'_{1/2}$ serum and hence about kidney function.

Measurements on man

Recently, we have had the opportunity of testing the use of this in vivo method on two of the Authors (KG, SS) who were given an injection of sodium metrizoate (Isopaque^R) in amounts corresponding to 350 mg of I per kilogram body weight. The tissue curve of contrast medium was evaluated in the tip of the forefinger. This choice is based partly on the fact that the tip of the forefinger is well perfused and partly that it is very practical to measure there, without inconvenience to the subjects. The iodine concentration in the forefinger was high enough to allow measurements up to more than 6 hours after injection. The measuring time in the period 2-4 hours after injection was 1 minute. The iodine concentration in serum 4 hours after injecting the contrast agent was approximately 200 $\mu\text{g/g}$. This corresponds to a net count rate

in the $I_{K_{\alpha}}$ -peak of (1500 ± 56) counts per minute when measuring in vivo on the finger tip. $T_{1/2}$ (finger) and $T'_{1/2}$ (serum) for KG and SS are listed in table 2. The correlation between $T'_{1/2}$ (finger) measured in vivo and $T_{1/2}$ (serum) measured in vitro is good. Measurements on a larger number of patients are in progress.

Clinical use of the X-ray fluorescence method for iodine detection in vivo implies a certain irradiation of a limited volume of the patient. Let us assume that we wish to calculate the elimination rate of contrast media by 6 measurements, each lasting 2 minutes, in the period 2-4 hours after injection of the medium. The total irradiation time will thus be about 12 minutes. The mean absorbed dose in the irradiated volume of the fingertips has been determined using TL-dosimeters in finger-like phantom and found to be 2.3 mGy (230 mrad). The total absorbed energy is estimated to be 0.003 mJ. This is negligible in comparison with that of an urography which gives 240 mJ (CARLSSON 1965) and also in comparison with that of a clearance determination with ^{51}Cr -EDTA which gives 0.8 mJ (KUNKEL and OBERHAUSEN, 1972).

SUMMARY AND CONCLUSION

Quantitative determination of the iodine concentration in the soft tissue of rabbits is possible by in vivo measurements using the X-ray fluorescence technique. The "normalized sensitivity", S_{nd} , which is the ratio between the net count rate of $I K_{\alpha}$ -X-rays (a) and the count rate (n) of primary photons incoherently scattered at around 90° , divided by the concentration shows good reproducibility. The influence on the measurements of variable factors such as weight is negligible, due to the use of a well-collimated geometry. The minor effect of geometrical changes during the measurements can be corrected for by using the

photons incoherently scattered at 90^0 as normalizing factor. The agreement between the biological half-lives of iodine containing contrast medium as measured in vivo in rabbit noses and in two humans and in vitro in serum during the period 2-4 hours after intravenous injection seems to be promising enough to justify the use of the in vivo measurement technique for clinical non-invasive evaluation of kidney function. We therefore intend to use this technique to determine the elimination rate of contrast medium from the fingers of patients after urography.

Table 1

Table 1a shows the results of I-concentration measurements in excised nose tissue samples as well as calculated individual calibration factors for the different rabbits.

In table 1b, the iodine concentrations in intact noses have been calculated from the individual in vivo measurements using the mean normalized sensitivity $\bar{S}_{nd}$

1a

Rabbit	Weight kg	I-concentration in tissue sample C_{ts} $\mu\text{g}\cdot\text{g}^{-1}$	Normalized sensitivity S_{nd} $(\mu\text{g}\cdot\text{g}^{-1})^{-1}$
1	1.75	27.0	$3.38\cdot 10^{-5}$
2	1.77	21.6	$3.16\cdot 10^{-5}$
3	2.30	70.2	$3.01\cdot 10^{-5}$
4	2.13	31.9	$3.09\cdot 10^{-5}$
5	2.00	121.2	$3.10\cdot 10^{-5}$
6	2.60	64.8	$3.18\cdot 10^{-5}$
7	3.10	52.8	$3.20\cdot 10^{-5}$
8	2.95	11.9	$3.42\cdot 10^{-5}$
9	1.96	599.0	$3.12\cdot 10^{-5}$

Mean value of normalized sensitivity ($\bar{S}_{nd}$): $(3.18\pm 0.13)\cdot 10^{-5}$

1b

Rabbit	R_{nd}	Estimated I-concentration in intact nose $C_{nd} = R_{nd}/S_{nd}$ $\mu\text{g}\cdot\text{g}^{-1}$
1	$9.70\cdot 10^{-4}$	30.5
2	$6.76\cdot 10^{-4}$	21.3
3	$2.00\cdot 10^{-3}$	62.9
4	$9.58\cdot 10^{-4}$	30.1
5	$3.65\cdot 10^{-3}$	114.8
6	$2.06\cdot 10^{-3}$	64.8
7	$1.69\cdot 10^{-3}$	53.1
8	$4.38\cdot 10^{-4}$	13.8
9	$1.81\cdot 10^{-2}$	569.2

Table 2 The values of $T_{1/2}$ finger measured in vivo
and $T'_{1/2}$ serum for two of the authors as
measured in vitro. The half-lives refer to
the period 2-4 hours after injection.

Subject code	$T_{\frac{1}{2}}$ (finger) min	$T'_{\frac{1}{2}}$ (serum) min
KG	87	92
SS	89	102

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FIGURE CAPTIONS

- Fig. 1 Experimental set-up for measuring the iodine concentration in the nose. The figure also shows a schematical pulse-height distribution from the detector. (a) means the net number of counts in the $I K_{\alpha}$ -peak and (n) the number of registered 90° incoherently scattered photons.
- Fig. 2 The elimination of iodine-containing contrast medium from soft tissue in the nose (in vivo) and serum (in vitro) for a rabbit.
- Fig. 3 The relation between the biological half-life, $T_{\frac{1}{2}}$, as measured in vivo in the nose of the rabbit and $T'_{\frac{1}{2}}$ as measured on serum in vitro. $T_{\frac{1}{2}}$ and $T'_{\frac{1}{2}}$ are determined from measurements 2 - 4 hours after the injection.

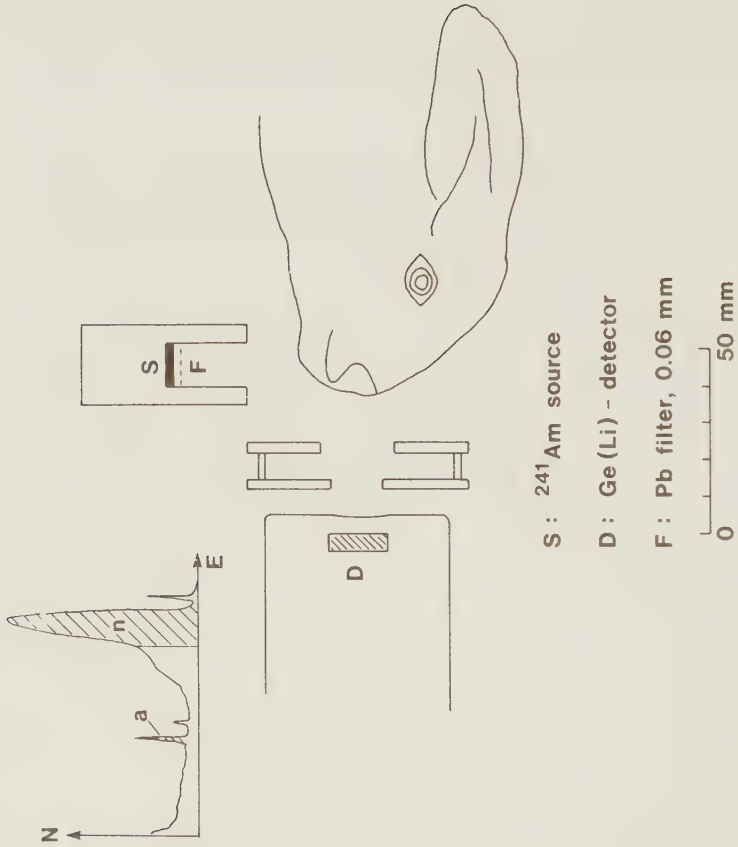


Fig. 1

Iodine concentration

$\mu\text{g} \cdot \text{g}^{-1}$

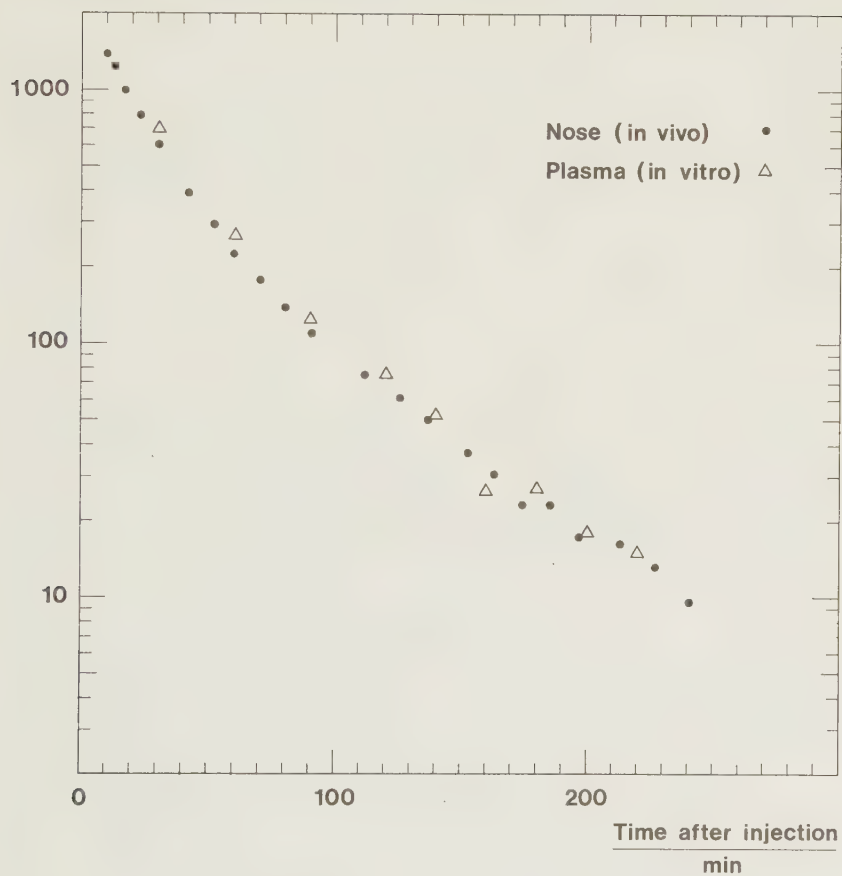


Fig. 2

$T'_{1/2}$ (plasma)

min

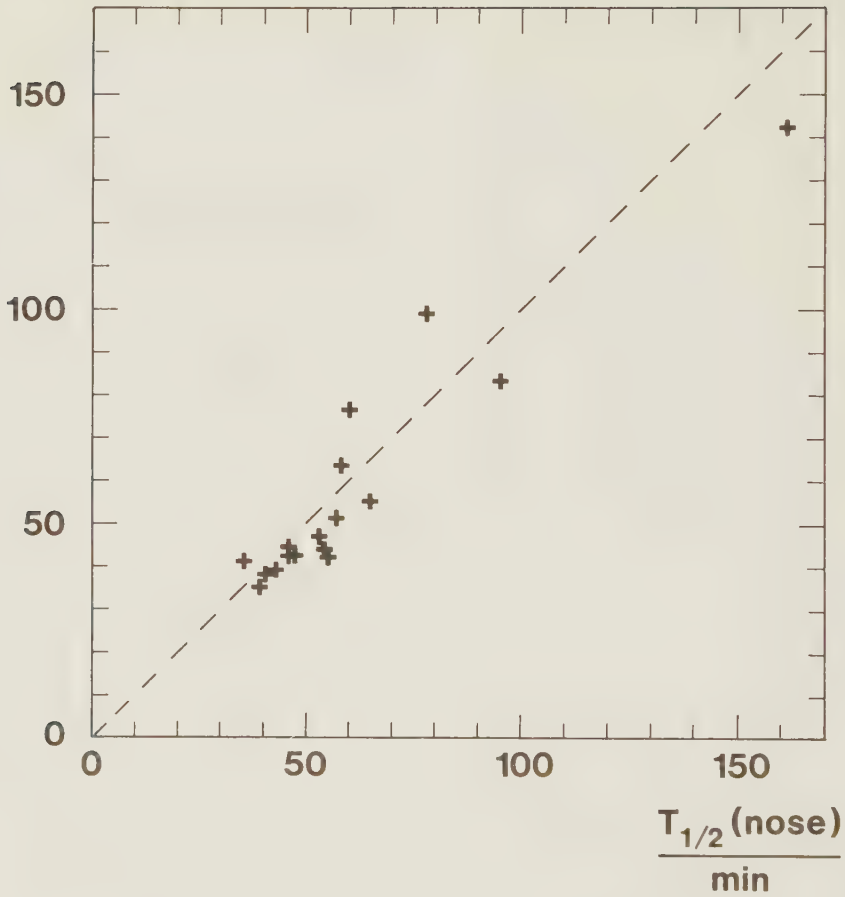


Fig. 3

NON-INVASIVE ESTIMATION OF KIDNEY FUNCTION BY X-RAY
FLUORESCENCE ANALYSIS

Elimination rate and clearance of contrast media in man

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ABSTRACT

A non-invasive method for the estimation of kidney function is described. The use of radioactive tracers and the sampling of plasma and urine are omitted. The method has been used in patients referred for urography and who had therefore been injected with routine amounts of iodine-containing urographic contrast medium. After urography, the elimination rates of urographic contrast medium from both serum and finger tissue were determined and compared during a two-hour period which began two hours after injection of contrast medium. The elimination of iodine in finger tissue was measured non-invasively using X-ray fluorescence analysis. A strong degree of correlation was found between the elimination rates from serum and finger tissue and between the total clearances calculated from the serum and finger measurements.

Thus, after urography estimation of kidney function may be obtained as a fringe benefit by external X-ray fluorescence measurements of the elimination rate of an iodine-containing contrast medium from tissue.

INTRODUCTION

Glomerular filtration rate is an important parameter in the evaluation of renal function. The reference method for the determination of glomerular filtration rate has been inulin clearance, which, performed in the classical way, requires constant infusion of inulin, several blood samples, catheterized urine sampling and difficult laboratory determinations of inulin.

To simplify analysis, labelled inulin or radioactive tracers with similar excretion mechanisms have been developed. Such markers are inulin-carboxyl- ^{14}C (1,2,3), inulin-methoxy- ^3H (1,2,3), ^{169}Yb -EDTA (3,4), ^{51}Cr -EDTA (3,4, 5,6,7,8,9,10) and $^{99}\text{Tc}^{\text{m}}$ -DTPA (3,11,12). Labelled urographic contrast media such as ^{125}I -iothalamate (3,12,13,14) and ^{131}I -diatrizoate (3,15,16) have also been used as markers.

To avoid urine sampling, the "single injection technique" (3,5,6,17,18,19) and the "single point method" (20) have been developed. These methods are based upon pharmacokinetic analysis of the elimination rate from serum of one of the injected markers mentioned above and requires one or more serum samples some hours after the injection.

To avoid taking plasma samples, these methods have been further developed by the use of external measurements of the elimination rates of radioactive tracers (3,21,22,23,24).

To avoid the use of radioactive tracers, X-ray fluorescence analysis of non-radioactive markers has been developed.

Non-radioactive iodine can be determined by means of X-ray fluorescence analysis both in vitro (25,26) and non-invasively in different organs in

the living organism. The method has been used for external determinations of the iodine content of the thyroid gland (27,28), of regional blood volumes in the brain (29) and of the cardiac output in the dog (30). In the latter two applications, an iodinated contrast medium was injected intravenously as a "tracer substance".

Koehler et al (31) used external X-ray fluorescence analysis to determine the iodine concentration in the liver of dogs after intravenous injection of meglumine iodipamide. They could follow the elimination of the contrast medium from the liver externally and found good correlation with in vitro determinations of the iodine concentration in liver homogenate.

Urography and renal angiography give no quantitative information of the function of the kidneys. The contrast media used routinely for these examinations are identical with those used in determinations of glomerular filtration rate (3,13,14,15,16,32). Guesry et al (33) and Alazraki et al (34) recognized this and used non-radioactive iothalamate as a marker for the determination of glomerular filtration rates, assaying the contrast medium in plasma samples by X-ray fluorescence analysis. Glomerular filtration rate determinations performed concurrently with urography using the injected contrast medium as a glomerular filtration rate marker have also been suggested (33). In previous experimental studies on rabbits (35,36) which had been intravenously injected with contrast media (500 mg iodine per kg body weight), it was possible to determine iodine concentrations in tissue (rabbit nose) with external measurements using X-ray fluorescence analysis. The elimination rates of iodine from tissue and serum were found to be similar.

Thus, estimation of kidney function by external X-ray fluorescence measurements of the elimination rate of iodine from well-perfused tissue in patients already injected with contrast media for roentgen diagnostic purposes was suggested (35,36).

The present investigation in man had the following four aims:

- To establish the detectability of iodine in peripheral tissue (patient finger tip) after intravenous injection of routine amounts of contrast medium using non-invasive in vivo X-ray fluorescence analysis, over an interval sufficiently long to permit the determination of an elimination curve which can be used to estimate kidney function.
- To investigate the possibility of using the area under the Compton contribution in the pulse-height distribution to correct for changes in measurement geometry caused by variations in shape, size and position of the finger measured.
- To compare the elimination rates of contrast medium obtained from iodine measurements in tissue and serum and to study the distribution of the individual conversion factors which are needed to transform the tissue data into serum iodine concentrations for total clearance calculations.
- To study the correlation between clearance values calculated from tissue measurements and from serum measurements.

MATERIALS AND METHODS

After a full explanation of the nature of the procedures, forty-four patients referred to the X-ray department for urography and two healthy persons volunteered to take part in the investigation. The material thus consisted of 46 subjects (mean age 56 years, range 16-86), including 11 women (mean age 46 years) and 35 men (mean age 59 years). The patients had various urological and nephrological diseases: none was confined to bed or had obvious edema. All subjects were prepared according to the Cascara-Salax method (37), routinely used for bowel cleansing in our X-ray department.

A plastic i.v. cannula (Venflon^R, Viggo AB, Sweden) was inserted into a superficial arm vein, preferably an antecubital vein, for contrast medium injection and blood sampling. To prevent clotting, it was flushed with 5 ml of heparinized saline (2 IU Heparin/ml in 0.9 % NaCl) at 15-20 min intervals or after each blood sampling. Intravenous urography was performed in each patient according to the patients diagnostic needs. The contrast medium was Isopaque^R 350 (Nyegaard & Co A/S, Norway) 350 mg I/ml, 1 ml/kg body weight. After urography, external X-ray fluorescence analysis of iodine was made during 1 - 2 minutes at the tip of the second finger of the left hand at 10 min intervals during the period 2 - 4 hours after the injection of contrast medium (Fig 1). At 30 min intervals in the same period, blood samples were drawn with disposable syringes. The blood was allowed to coagulate and was then centrifuged. The serum (0.5 ml) was transferred with pipettes to plastic tubes (OD / ID 1.00/0.87 cm) and iodine was analyzed using X-ray fluorescence.

In the interval between urography and the X-ray fluorescence measurements, the subjects were allowed to eat a sandwich and drink two glasses of milk or juice. They were at rest, sitting or lying down on a couch. The X-ray fluorescence measurements were made with the subjects supine on a couch. The fore finger of the left hand was put into a finger holder as shown in Fig 1. To generate the characteristic X-rays of iodine (K_{α} :28.5 keV) in the finger, a disc-shaped well-collimated ²⁴¹Am radionuclide source (11 GBq) was used. The collimator in front of the source and the radiation shield were made of pure lead. To reduce the fluence rate of low energy photons emitted from the source, a 0.06 mm thick lead filter was placed in front of it.

The secondary radiation was studied at 90° to the direction of the incident photons from the source by means of a high-purity (16 mm (diam) x 5 mm) Ge-detector (Princeton Gamma-tech, Frankfurt, West Germany). The

collimator used in front of the detector was made of copper covered with tantalum foils. The detector was connected via a pulsed optical feed-back preamplifier and a pulse-shaping linear amplifier to a 80 MHz analog-to-digital converter. A base-line restorer was used to maintain the energy resolution at the high count-rates used ($\approx 10^4 \text{ s}^{-1}$).

A typical pulse-height distribution of photons emitted from the finger tip is given in Fig 1. The geometry used for the in vitro measurements of the serum samples was almost identical to that shown in Fig 1.

Serum measurements:

The iodine concentrations of the serum samples (0.5 ml) were determined from the net count rate a_s^* in the $I_{K_{\alpha}}$ -peak (Fig 1) and a calibration curve obtained from measurements on aqueous solutions with known iodine concentrations in the interval 5 - 3000 $\mu\text{g/g}$.

In each of the 46 subjects, the logarithm ($\epsilon\log$) of the iodine concentration in serum was plotted as a function of time after injection. With the assumption that elimination of the contrast agent from serum in the time interval 120 - 240 min after injection can be described by a single exponential function (single injection technique, one-compartment model (3)), the elimination rate constant β_s' and the intercept k_s' were determined by a least-squares exponential curve fit. The iodine concentration in serum (C_s') as a function of time (t) after injection is given by equation 1.

$$C_s'(t) = k_s' \cdot e^{-\beta_s' \cdot t} \quad (120 \leq t \leq 240) \quad 1$$

Finger measurements:

(1) The net count rate, a_f , in the $I_{K_{\alpha}}$ -peak obtained from the finger measurements is proportional to the amount of iodine in the volume of the ir-

* prime denotes test tube measurements
 index s denotes serum data
 index f denotes finger tip data

radiated finger seen by the detector. The number of counts per minute from primary photons scattered at around 90° in the fingertip, n_f , is proportional to the mass of the fingertip volume. In the first 14 patients, both a_f and $(a/n)_f$ were plotted against t in a semilogarithmic diagram. The quotient $(a/n)_f$ was used to correct for small changes in the amount of tissue irradiated. The validity of this correction was studied by comparing the coefficients of determination $r_{a_f}^2$ and $r_{(a/n)_f}^2$ after a least-squares exponential curve fit.

(2) Analogous to the serum measurements, in each of all 46 subjects, the exponential curve fit obtained from the measured values of $(a/n)_f$ as a function of time gave the elimination rate constant β_f and the intercept k_f .

$$(a/n)_f(t) = k_f \cdot e^{-\beta_f \cdot t} \quad 120 \leq t \leq 240 \text{ min} \quad 2$$

For all 46 subjects, β'_S was plotted against β_f . A linear regression was performed using the least-squares method and the correlation coefficient determined.

Conversion factor

To be able to convert finger measurement data to iodine concentrations in serum, a conversion factor S was determined at $t = 180$ min using equation 3.

$$S = \frac{(a/n)_f(180)}{C'_S(180)} = \frac{k_f \cdot e^{-\beta_f \cdot 180}}{k'_S \cdot e^{-\beta'_S \cdot 180}} \quad 3$$

The mean value ($\bar{S}$) and the standard deviation of S for 46 subjects were calculated. The minimum detectable concentration (MDC) of iodine in serum in measurements on the finger tip was determined from measurements on the two normal volunteers. By definition, according to equation 4 (38), this is

$$MDC = \frac{3 \cdot C'_S \cdot \sqrt{b_f \cdot t_x}}{a_f \cdot t_x} \quad 4$$

where b_f is the background-count-rate in the I_{K_α} -peak and t_x the measuring time related to MDC.

Total clearance calculations

Using the single injection technique and applying the one compartment model (3), the total clearance (Cl) in the time interval $120 \leq t \leq 240$ min was calculated:

a) serum data:

$$Cl'_S = \frac{Q_0 \cdot \beta'_S}{k'_S} \quad 5$$

b) finger data:

$$Cl_f = \frac{Q_0 \cdot \beta_f}{(k_f/\bar{S})} \quad 6$$

where Q_0 is the amount of iodine injected.

All clearance values were normalized to 1.73 m^2 body surface, using the factor $(1.73/\text{surface area})$. The body surface area was calculated according to Boyd (39).

For the total material, Cl'_S was plotted against Cl_f . Linear regression was performed using the least-squares method and the correlation coefficient determined.

Computer programme

An eight-bit micro-computer (zilog Z80) with a memory capacity of 16 k RAM, was connected to the analyzing system in order to simplify the calculations and for administration of the examinations.

In figure 2 the flow-diagram used to program the micro-computer is given. This program is able to administrate two patients at once. Some of the boxes in the flow diagram may require a few comments.

Box 1: Input of patient data

- a) date of examination
- b) name of patient
- c) date of birth
- d) height (m)
- e) weight (kg)
- f) amount of iodine injected (mg)
- g) time of contrast medium injection (h,min) t_0

Box 2-3: The internal clock is set to real time t and in this loop a test is made to see if the time t is equal to $t_0 + 120 \times \Delta \cdot N$, where Δ is the time span between two measurements in minutes and N denotes the number of measurements performed.

Box 6,7,8: When a measurement is finished, the following information is automatically transferred to the computer:

- a) Measuring time interval t_m (s)
- b) The total area of the I_{K_α} -peak, P_f^x (counts)
- c) The background under the I_{K_α} -peak, b_f^x (counts)
- d) The primary photons, n_f^x (counts) compton scattered at around 90°

The quantities P_f^x , b_f^x and n_f^x are multiplied by $60/t_m$ which means that they are given in terms of counts per minute (P_f , b_f , n_f). The net count-rate a_f is given by $P_f - b_f$ and the dimensionless ratio $(a/n)_f$ is calculated.

After each measurement, the values of t, t_m, a_f, n_f and $(a/n)_f$ are stored.

Box 9,10: If the number of measurements is greater than or equal to 3, the values β_f , k_f and $r_{(a/n)_f}^2$ are calculated and displayed.

Box 12: If $\Delta \cdot N \geq 120$, the examination of this patient is terminated.

Box 13: The entire examination is stored on tape and the data may be studied later on, e.g. in graphical form.

Box 14: As mentioned above, parallel examination of two patients could be performed. When the second patient is started, t_0 is corrected so that the time-difference between the measurements on patients 1 and 2 is maximized. This means that if Δ is 10 minutes, patient 2 might be examined in the time-interval 125-245 minutes instead of 120-240 minutes after the injection.

RESULTS

The iodine concentration in serum four hours after the injection of contrast medium was approximately 200 $\mu\text{g/g}$ for the two subjects with known normal kidney function. Measured externally on the finger tip, this corresponds to a net count rate in the $I_{K\alpha}$ -peak of 1500 ± 65 counts/min⁻¹. The minimum detectable amount of iodine in the finger tip corresponds to a concentration of about 14 $\mu\text{g/g}$ in serum for a measuring time of 1 min.

The mean values of the coefficients of determination r_{af}^2 and $r_{(a/n)_f}^2$ obtained from studies on 14 patients were 0.95 ± 0.04 and 0.98 ± 0.01 respectively. Since $(a/n)_f$ gave a better fit to the curve than the former, this quotient was used for the finger measurements in all subjects.

Fig 3 shows the iodine elimination curves for the two normal subjects as measured externally on the finger tip and on serum samples.

The correlation between the elimination rates in serum and finger, β'_S and β_f , is shown in Fig 4. The equation obtained from linear regression is $\beta'_S = 0.83 \beta_f + 1.54$; $r = 0.88$.

The distribution of $S (\mu\text{g/g})^{-1}$, where S is the factor used to convert the finger measurement data to absolute serum concentration, is given in Fig 5.

Assuming that S is normally distributed, which is supported by the histogram in Fig 5, the mean value $\bar{S}$ and the standard deviation were determined to be $1.27 \cdot 10^{-5} (\mu\text{g/g})^{-1}$ and $0.18 \cdot 10^{-5} (\mu\text{g/g})^{-1}$ respectively.

The correlation between total clearances calculated from serum and from finger data, Cl'_S and Cl_f , is shown in Fig 6. The equation obtained from linear regression is $Cl'_S = 0.95 Cl_f + 6.92$; $r = 0.94$.

DISCUSSION

With the equipment used, we found it easy to follow iodine elimination in the finger tips of all patients throughout the entire period of interest, even in subjects with normal renal function (35,36). The counting statistics show that it should be possible to reduce the amount of contrast medium or to increase the interval between injection and measurement period. The relatively good curve fit obtained, using only the area under the I_{K_α} -peak, (a_f), as a measure of the iodine content in the finger tip, indicates a fairly stable measurement geometry. However, the fit somewhat improves when primary photons n_f scattered at around 90° are used to correct for small changes of the irradiated volume seen by the detector.

The elimination curves for iodine in serum and the elimination curves for iodine in the finger tip in the two normal subjects are given in Fig 4. A brief discussion of the elimination curves is given below. After the injection of contrast medium, the serum concentration of iodine depends on the distribution of the medium in different kinds of interstitial spaces, the glomerular filtration and a very small biliary excretion. The serum curve may at some time t be expressed by

$$C_s(t) = u_1 e^{-\beta_1 t} + u_2 e^{-\beta_2 t} + \dots + u_n e^{-\beta_n t} \quad 7$$

Here, $u_1 \dots u_n$ are weighting factors and $\beta_1 \dots \beta_n$ are rate-constants. If the renal function is not seriously impaired, the rate-constant representing the glomerular filtration will after some time t_s dominate to a degree which makes it possible to apply a single-compartment open model and to express the serum iodine retention curve as a single exponential function, i.e., $C_s = k_s e^{-\beta_s \cdot t}$.

The iodine concentration in the interstitial space (C_{is}) represented in the finger tip as well as the serum concentration may be expressed as a sum of exponential functions:

$$C_{is}(t) \sim v_1 e^{-\beta_1 t} + v_2 e^{-\beta_2 t} + \dots + v_n e^{-\beta_n t} \quad 8$$

It must be noted here that while $\beta_1 \dots \beta_n$ are the same as in the serum case, the weighting factors $v_1 \dots v_n$ are not. When measuring on the finger tip, the result $(a/n)_f$ will be a linear combination of $C_s(t)$ and $C_{is}(t)$ according to:

$$(a/n)_f(t) \sim g C_s(t) + h C_{is}(t) \quad 9$$

In this equation, g and h are geometrical weighting factors representing the relative influence of the irradiated volume of blood and of the interstitial space, seen by the detector. This may be written as:

$$(a/n)_f(t) \sim (g u_1 + h v_1) e^{-\beta_1 t} + \dots + (g u_n + h v_n) e^{-\beta_n t} \quad 10$$

In the same way as in the serum measurements, this means that the rate-constant β_s representing the glomerular filtration will dominate after some time t_f . Due to the different weighting factors, t_f may be less than, equal to or greater than t_s . We have assumed that t_s is approximately 120 min (6) and in Fig 3 it is shown that t_f for the two normal subjects is about 50-70 min.

The correlation between β_f and β_s shown in Fig 4 shows that β_s is greater than β_f for the majority of the patients. This might indicate that t_s has not yet been reached after 120 min. Others (40) have suggested that the

slope of the serum retention curve should not be related to the glomerular filtration rate until 180 min after the injection. The conversion factor $S \text{ (}\mu\text{g/g)}^{-1}$ is needed to estimate the total serum clearance from the finger measurements. The distribution of S is given in Fig 5. The standard deviation in this distribution is $\pm 14\%$ and it should be possible to use the mean value of the distribution as a conversion factor. If the standard deviation is considered to be too large, one blood sample taken in the middle of the measurement period is enough to determine an individual conversion factor.

The correlation between the total clearance values obtained from the finger measurements and from the serum measurements shows that the uncertainty in estimating the total serum clearance from the finger measurements is $\pm 15\text{-}20\%$. However, the slope of the regression line does not differ significantly from 1 and it is therefore possible, within these limits of uncertainty, to estimate the total serum clearance from finger measurements as described above.

The one-compartment open model used to calculate the total clearance in this work has theoretical drawbacks (6). Others (6) have found it possible to use this simple model and to apply corrections to eliminate the underestimating of the area under the serum retention curve which leads to an overestimate of the total clearance. Such corrections must be dependent on the particular substance used as a tracer and a thorough knowledge of the initial serum curve profile is necessary. We have only been able to study the initial curve profiles in two healthy volunteers, which does not give enough information to derive a correction procedure. It should be possible to make this correction. This, however, does not improve the precision of finger versus serum determinations, but only the accuracy of the total clearance determination.

Since they are also excreted through the liver, contrast media are not ideal renal clearance markers. This contribution to the total clearance,

is relatively small in subjects with normal renal function as only 1-2 % of the injected amount is excreted with the faeces, but in subjects with seriously impaired renal clearance, the biliary excretion becomes a greater part of the total clearance. Due to the biliary excretion, the evaluation of renal function from the total clearance of contrast media thus gives an overestimate, significant only at low renal clearance values.

If six X-ray fluorescence measurements of the finger tip are considered necessary in order to calculate the total clearance of contrast medium, the mean absorbed dose in the finger irradiated has been measured to be 2.3 mGy (230 mrad) (35). The finger tip was chosen as the site of external X-ray fluorescence measurements since it is easily accessible. About 30 per cent of the finger volume is composed of subcutaneous tissue and skin and there are a large number of arteriovenous anastomoses in the skin (42).

Of the total blood flow through the finger, the greater part normally passes through the skin while it can vary with thermal and emotional stimuli, such variations are, however, transient and normally the blood flow to the skin is considerably in excess of its metabolic requirements (42). The good fit obtained from the external X-ray fluorescence measurements does not indicate any disturbances attributable to variations in the blood flow through the fingers of the subjects who were at rest at normal room temperature throughout the measurement period.

CONCLUSION

By means of external X-ray fluorescence measurements on the finger tip, it is possible to follow the elimination of urographic amounts of iodine-containing contrast medium from finger tissue throughout the period of interest.

A strong correlation exists between the elimination rates of contrast medium from finger tissue and serum.

This shows the possibility of using external X-ray fluorescence measurements of the elimination from tissue of iodine-containing contrast media given for radiographic purposes as a method of estimating kidney function.

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FIGURE CAPTIONS

- Figure 1 Experimental arrangement for measuring the amount of iodine in the finger tip. The figure also shows a schematical pulse height distribution from the detector. (a) denotes the net number of counts min^{-1} in the $I K_{\alpha}$ peak and (n) the number of registered primary photons incoherently scattered at around 90° .
- Figure 2 Flow diagram used to programme the computer in order to administer the examinations and perform calculations.
- Figure 3 The elimination of iodine-containing contrast medium from soft tissue in the finger tip (in vivo) and serum (in vitro) for two healthy volunteers. The finger data are normalized to the serum curve by means of $\bar{S}$.
- Figure 4 The relation between the elimination rate constant β_f , as measured (in vivo) on the finger tip, and β'_s , as measured on serum (in vitro). β_f and β'_s are determined from measurements 2-4 h after injection.
- Figure 5 The distribution of the individual conversion factors S. The mean value $\bar{S}$ of the distribution has been used to convert finger measurement data to iodine concentrations in serum.
- Figure 6 The relation between Cl_f , the clearance value as measured (in vivo) on the finger tip, and Cl'_s as measured on serum (in vitro). Cl_f and Cl'_s are determined from measurements 2-4 h after injection.

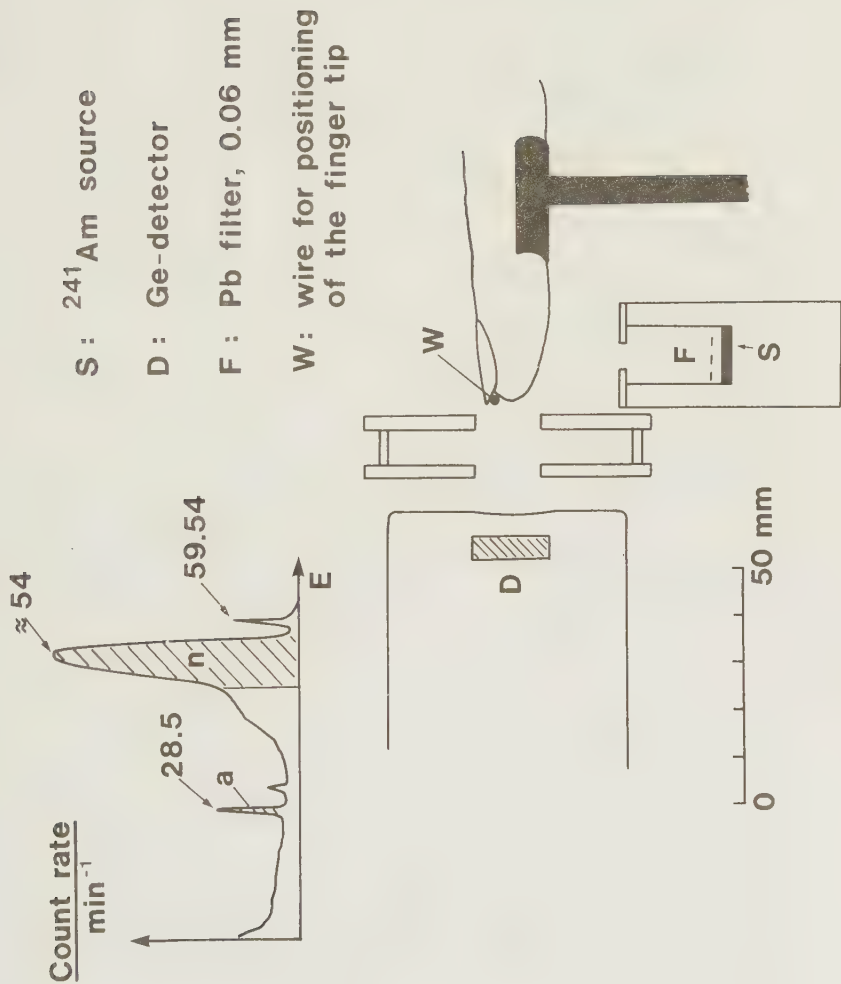


Fig. 1

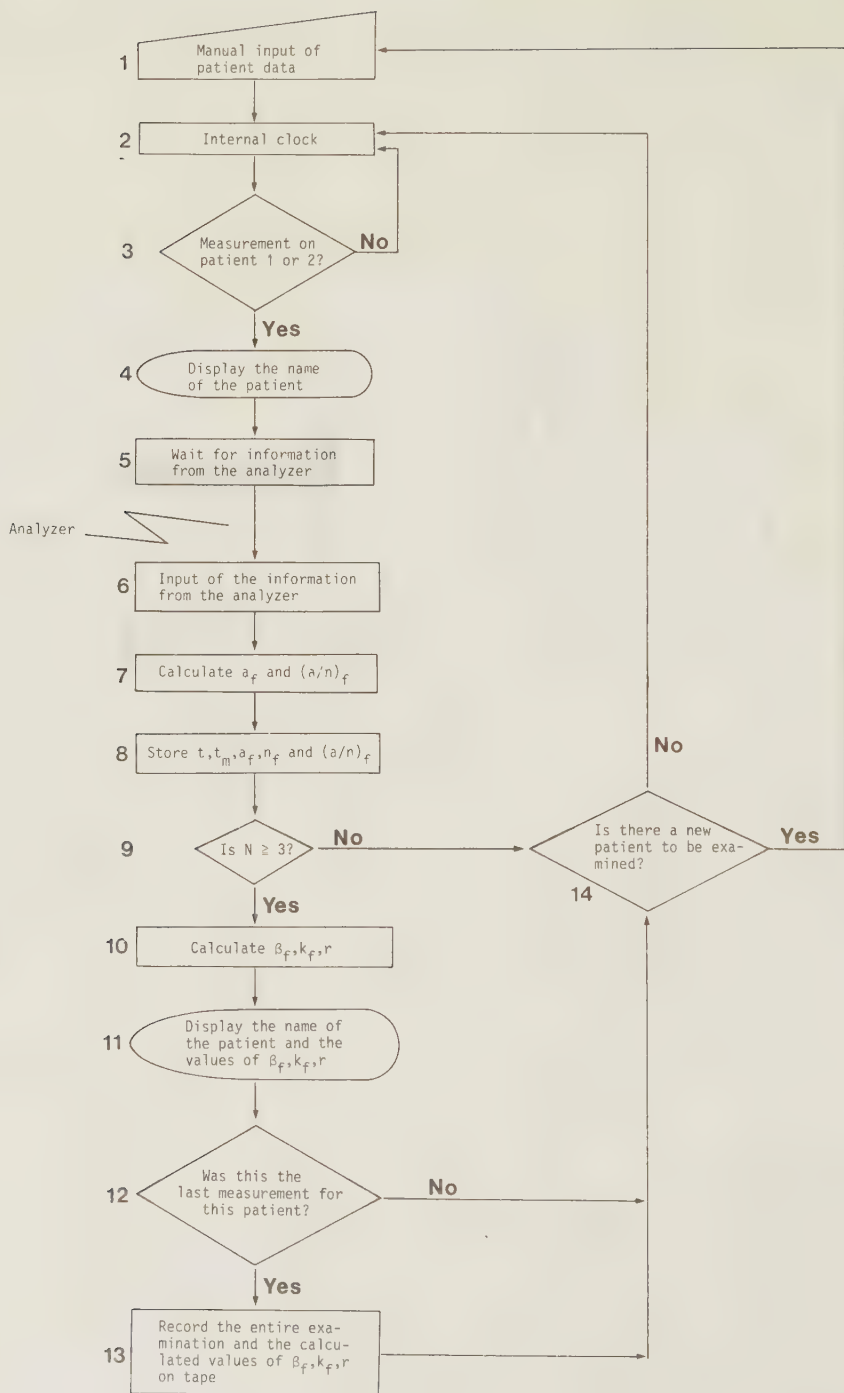


Fig. 2

I-concentration

$\mu\text{g/g}$

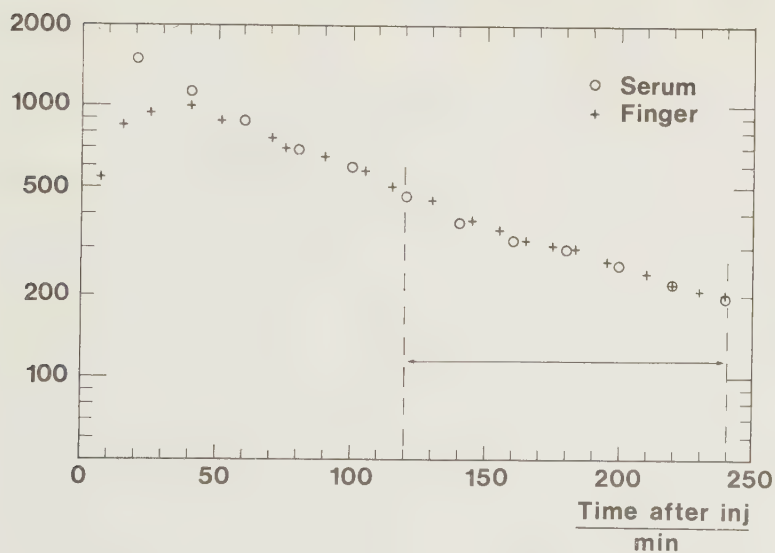
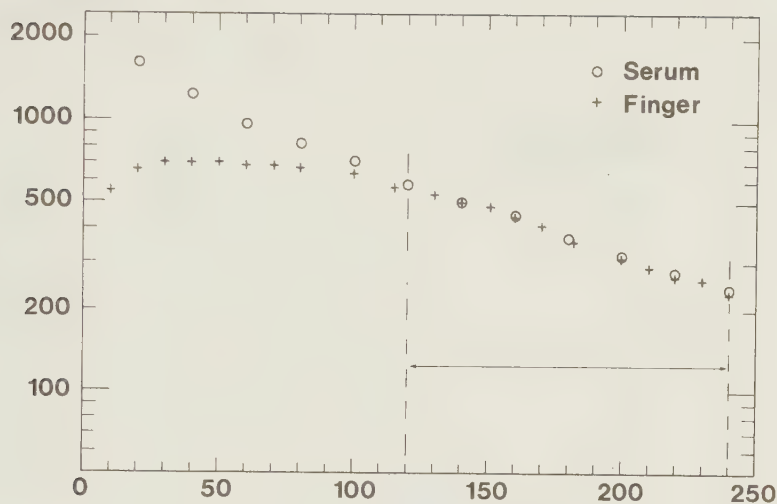


Fig. 3

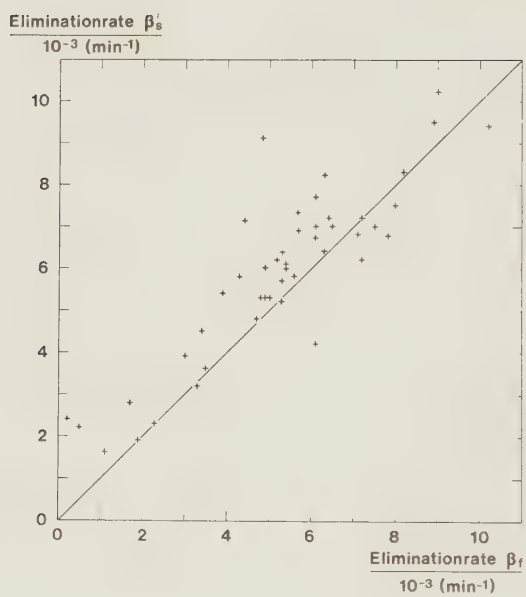


Fig. 4

Number of subjects

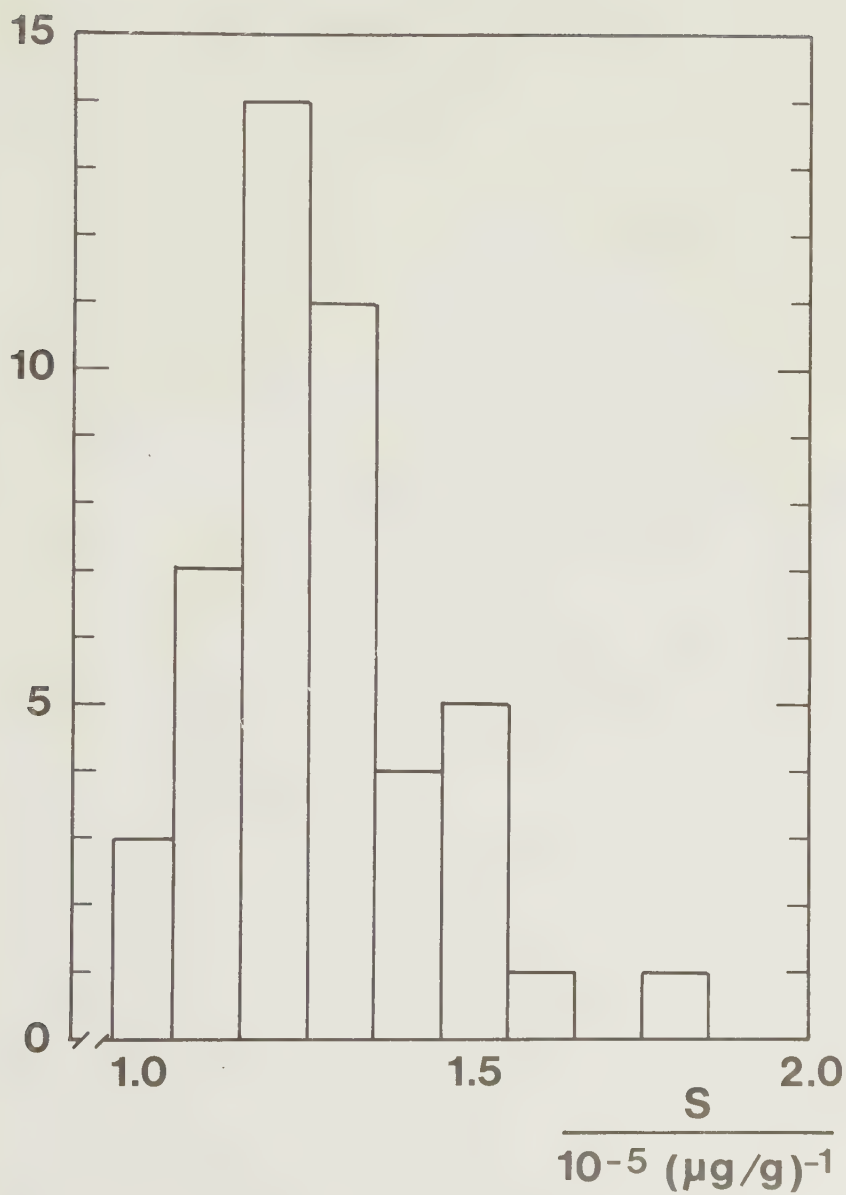


Fig. 5

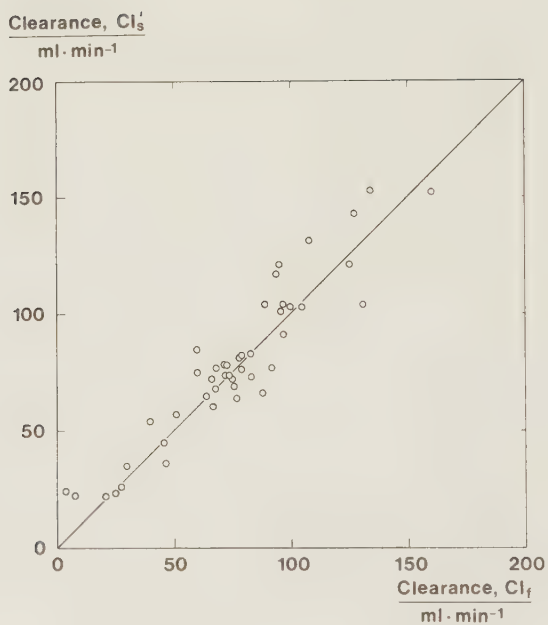


Fig. 6

